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Original Research Article

High-throughput inhibitor screening and molecular dynamics simulation studies against Human JAK2

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Abstract

Purpose: *To investigate the lead molecule for inhibition of JAK2 using high-throughput screening and molecular dynamics simulation.*
Methods: *The MCULE database was used to screen 5 million ligands in a structure-based mode. The ligand hits were ranked according to VINA scores. Further filtration was achieved by approaches like MCULE-Toxicity Checker, Zero-RO5-Violation-Check, synthetic accessibility and overall pharmacokinetic features. Stability of the JAK2-inhibitor-complex was confirmed by molecular dynamics simulation of 120 ns, which used the AMBER14 force field in YASARA Structure-21.8.27. W.64.*
Results: *The top molecule, 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d) pyrimidin-7-yl), demonstrated strong binding with JAK2 involving 17 amino acid residues, 16 of which overlapped with the reference (PDB: 3JY9). It successfully passed all screening tests. The RMSD-time plot indicated that equilibrium was reached around 20 ns. Throughout the simulation from 20 to 120 ns, the backbone RMSD fluctuations remained within a narrow range of 1.0 – 1.7 Å.*
Conclusion: *The ligand, 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d) pyrimidin-7-yl), meets the ADMET criteria. Also, an extended 120 ns Molecular Dynamics Simulation confirms the feasibility of the 'JAK2-Top ligand' complex. This ligand is a promising lead for designing inhibitors against JAK2 and should be further evaluated in future laboratory experiments.*

Keywords: *JAK2, High throughput virtual screening, Molecular Dynamics Simulation, Versatile therapeutic target*

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INTRODUCTION

The Janus family kinases (JAKs) represent a group of versatile therapeutic targets. The JAK inhibitors have been studied for application in the treatment of cancer, inflammatory diseases such as rheumatoid arthritis, various skin conditions, genetic red blood cell (RBC) disorders such as ß-thalassemia and recently, COVID-19 [1,2]. Therapeutic targeting of JAKs is important in various disciplines, including oncology, dermatology, hematology, rheumatology and novel challenging diseases like COVID-19 [2]. Short-term dosing of JAK2 inhibitors diminishes splenomegaly in animal models of β-thalassemia intermedia and major. Reports suggested a strong rationale for therapeutically targeting JAKs, particularly JAK2 [2]. The term, enzoinformatics is

increasingly used in scholarly publications. According to Shakil *et al* [3], it is a subfield of bioinformatics that specifically focuses on interactions between enzymes and ligands. The significance of *in silico* lead discovery studies is that these reports lessen the burden on scientists involved in wet laboratory work, as they unveil reasons to reject irrelevant small molecules from the starting set. Current studies have elucidated molecular interactions for several important therapeutic targets, including matrix metalloproteinases [4], acetylcholinesterase, butyrylcholinesterase [5], CTX-M-15 [6], CTX-M-14 [7], Sodium-Glucose and Co-transporter 2, SHV [8].

Various ligands such as Dapagliflozin [9], Lycodine [10], Glimepiride [11], and Methotrexate, Sotagliflozin [8]. It has been established that JAK2 inhibitors are used in the treatment of various diseases. This study, therefore, investigated molecular dynamics simulation and high-throughput screening to identify a more effective lead drug for JAK2 inhibition.

EXPERIMENTAL

Binding site examination

The RCSB Protein Data Bank item with accession code 3JY9 was chosen as the reference complex. It shows the crystal structure of the JAK2 protein in combination with cycloocta(1,2,3-cd) and (3S)-3-(4-hydroxyphenyl)-1,5-dihydro-1,5,12-triazabenzo [4,5]. inden-4(3H)-one. YASARA Structure 21.8.27.W.64 and Discovery Studio Visualizer (BIOVIA) were used to investigate the binding site's three-dimensional structure in this crystal [12].

High-throughput computational screening

A high-throughput fundamental assessment of 5 million test molecules as potential JAK2 inhibitors was conducted using the structure-based mode in MCULE [13]. This was accomplished by using the MCULE platform workflow builder. To allow for initial search flexibility, one violation of the Rule of Five was permitted in the Basic Property Filter. Parameters such as a maximum of 9 rotatable bonds, a minimum of 1 hydrogen-bond donor, and a sample size of 1000 were set. The threshold similarity cut-off was set at 0.7, and there could be no more than 100 of the most diverse molecules. Other parameters were maintained at their default values in the workflow builder. Molecular descriptor analyses were performed using OBLF, resulting in a maximum of 3 million compounds post-sphere-exclusion.

Docking of JAK2 with test ligands

The 3-D structure of the JAK2 protein (in PDB format) was retrieved from PDB ID 3JY9 and fetched to the MCULE platform using Discovery Studio Visualizer (BIOVIA). Docking was carried out using VINA on the platform [14]. A 60 $Å^3$ docking grid was employed, with input values of 12.769550 for x, 13.522739 for y, and 2.860078 for z coordinates of the grid position. These values were determined by closely inspecting the reference crystal structure (PDB ID: 3JY9).

The VINA docking score cut-off, toxicity checking and zero RO5 violation

The 95 ligands from the VINA docking output's top layer were further examined. Test molecules with a VINA docking score higher than -8.2 kcal/mol were eliminated. The MCULE toxicity checker further reduced the number of remaining molecules. Only non-toxic compounds that adhered to the established RO5 rule were retained.

Overall pharmacokinetic features

The pharmacokinetic profiles of test ligands were generated using SWISS ADME [15]. The compounds were subjected to various filters, including Lipinski [16], Ghose [17], Veber [18], Egan [19], Muegge, PAINS, and Brenk filters to assess their potential as future medications. These filters evaluate characteristics such as lead-likeness, synthetic accessibility, rotatable bond count, and gastrointestinal absorption. The Top anti-JAK2 ligand identified in the current study was a JAK2 inhibitor that met the criteria of no RO5 violation, no violation of lead-likeness, and was deemed non-toxic. This compound exhibited the most suitable features according to the lead finding cascade provided.

Analysis of molecular overlays and ligand interactions for JAK2-top ligand complex

The binding site residues that demonstrated a significant interaction with the Top anti-JAK2 ligand in the bound state were identified using Discovery Studio Visualizer. Furthermore, the JAK2-top ligand complex was superimposed on the reference PDB crystal (PDB ID: 3JY9) for comparison.

Molecular dynamics simulation using 120 ns YASARA structure

Molecular dynamics simulation was used to assess the stability of the top putative inhibitor while binding to JAK2. The YASARA version

21.8.27.W.64 was employed to analyze the trajectory using the AMBER14 force field over a 120 ns period. The simulation was conducted using a previously reported approach [20].

RESULTS

The binding site

Molecular analysis of 3-D structure of the binding crevice in the reference crystal (PDB ID: 3JY9) revealed that 17 amino acid residues were essential for ligand positioning. These were Gly 993, Asp 994, Leu 902, Glu 898, Leu 927, Phe 995, Met 929, Lys 882, Leu 855, Val 911, Ala 880, Leu 983, Tyr 931, Leu 932, Val 863, Gly 856 and Glu 930.

Screening output

The screening cascade was exemplified on the 3-D structure of the JAK2 protein. In this study, over 5 million test ligands were investigated to assess their binding to JAK2 as the target. As a result, 95 potential JAK2 inhibitors were identified (Figure 1).

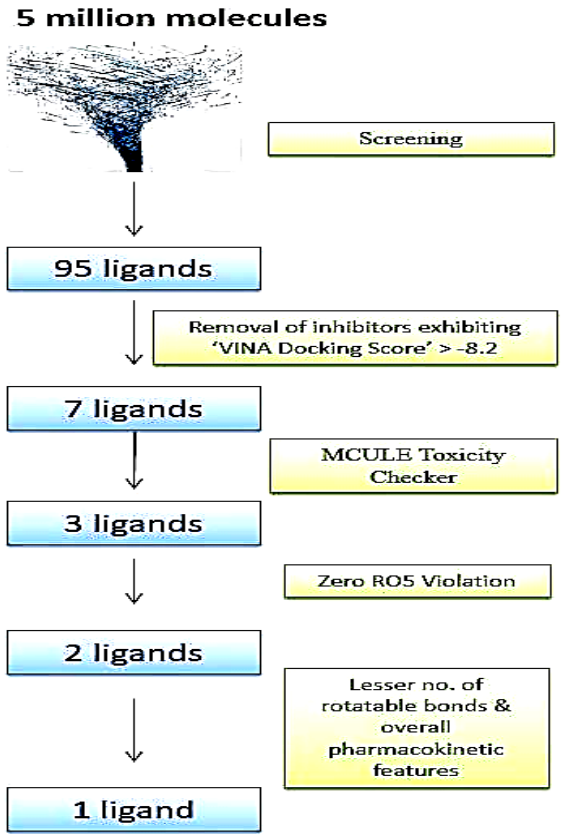


Figure 1: Outline of the ligand screening cascade against JAK2 enzyme as the target

Ranking by VINA scores, outcome of toxicity tests and zero RO5 violation filter

A higher VINA docking score indicated a better fit for the protein-ligand pair. In this manner, 95 ligands that comprised the creamy layer of the VINA docking output were selected for further filtration (Figure 2).

Outcome based on overall pharmacokinetic features

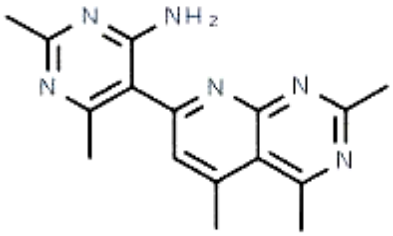
The SMILES notations of the two remaining ligands, MCULE-4752895944-0-236 and MCULE-7590816301-0-111, were sent to CHEMSPIDER in order to provide corresponding IUPAC names. MCULE-7590816301-0-111 and MCULE-4752895944-0-236 were determined to have the IUPAC names 4-(4-Methyl-1-piperazinyl) and 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5- trimethylpyrido (2,3-d) pyrimidin-7-yl), respectively.

A closer comparison revealed that MCULE-4752895944-0-236 had an edge over MCULE-7590816301-0-111. Generally, a ligand having lesser number of rotatable bonds is preferred in drug design. MCULE-4752895944-0-236 was found to have just 1 rotatable bond. A lower value of the synthetic accessibility score was preferred as it implies ease of synthesis (3.03 for MCULE-4752895944-0-236). Furthermore, MCULE-4752895944-0-236 displayed absolute zero violation of lead-likeness while MCULE-7590816301-0-111 also displayed violation (1 violation: XLOGP3 > 3.5; Table 1). In this study, MCULE-4752895944-0-236, also known as 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d)pyrimidin-7-yl)-, was identified as the top anti-JAK2 ligand.

Binding interactions and overlay analyses

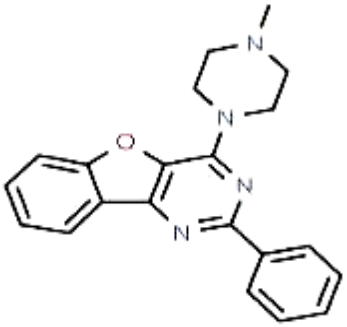
The 2-D diagram of the top ligand (MCULE-4752895944-0-236) attached to the JAK2 enzyme is displayed in Figure 3. Discovery Studio Visualizer was utilized to identify the binding site residues crucial for interaction with the top anti-JAK2 ligand in the bound state. The JAK2 protein was found to bind to 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d)pyrimidin-7-yl), the top anti-JAK2 ligand, through 16 amino acid residues. Remarkably, 16 of the 17 binding residues coincided with the protein-ligand interaction displayed by the reference complex (PDB: 3JY9).

(i) MCULE-4752895944-0-236



2,6-Dimethyl-5-(2,4,5-trimethylpyrido[2,3-d]pyrimidin-7-yl)-4-pyrimidinamine

(ii) MCULE-7590816301-0-111



4-(4-Methyl-1-piperazinyl)-2-phenyl[1]benzofuro[3,2-d]pyrimidine

Figure 2: Structures of the (ID: MCULE-7590816301-0-111) obtained by the high-throughput ligand screening against JAK2 enzyme

Table 1: Pharmacokinetic profiles of the top two putative JAK2 inhibitors generated by SWISS ADME

Ligand feature	MCULE- 4752895944-0-236	MCULE-7590816301-0- 111
IUPAC Name	4-pyrimidinamine, 2,6- Dimethyl-5-(2,4,5- trimethylpyrido(2,3-d)pyrimidin-7-yl)-	4-(4-Methyl-1-piperazinyl)- 2-phenyl(1)benzofuro(3,2-d)pyrimidine
Formula	$C_{16}H_{18}N_6$	$C_{21}H_{20}N_4O$
Molecular Weight (g/mol)	294.354	344.41
LOG S (Ali)	-3.9	-4.61
'Rule of Five' violations	0	0
H-bond acceptors	5	4
H-bond donors	1	0
Rotatable bonds	1	2
Topological Polar Surface Area (TPSA; Å²)	90.47	45.40
Molar Refractivity	87.59	111.01
Gastrointestinal Absorption	High	High
Synthetic accessibility	3.03	3.33
Drug-Likeness and Medicinal Chemistry Filters		
Lipinsky (Pfizer)	YES	YES
Ghose	YES	YES
Veber (GSK)	YES	YES
Egan (Pharmacia)	YES	YES
Muegge (Bayer)	YES	YES
PAINS	YES	YES
Brenk	YES	YES
Lead-Likeness	YES	NO; 1 violation: XLOGP3 > 3.5

These 16 common residues were found to be Gly 993, Asp 994, Leu 902, Glu 898, Leu 927, Phe 995, Met 929, Lys 882, Leu 855, Val 911, Ala 880, Leu 983, Tyr 931, Leu 932, Val 863 and Gly 856. This further confirms the precision of the docking experiments. Also, for visual comparison, the reference PDB crystal (PDB ID: 3JY9) was superimposed with the JAK2-top ligand complex. The molecular overlay illustration of the JAK2-top ligand multifarious is displayed in Figure 4 in relation to the 3JY9 reference crystal. It can be inferred from Figure 4 that the top anti-JAK2 ligand obtained via the screening cascade and the ligand of the reference complex (PDB: 3JY9) bind exactly at the same spot.

Outcome of molecular dynamics simulation of 120 ns

The JAK2 complex bound to the top ligand, 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d)pyrimidin-7-yl), underwent a 120 ns molecular dynamics simulation using YASARA structure v. 21.8.27. The trajectory was analyzed using AMBER14, with snapshots taken at 250 ps intervals, resulting in 496 snapshots. Various graphs and images were generated, including a ray-traced diagram of the JAK2-top ligand complex and the top anti-JAK2 ligand, a plot of potential energy versus simulation time,

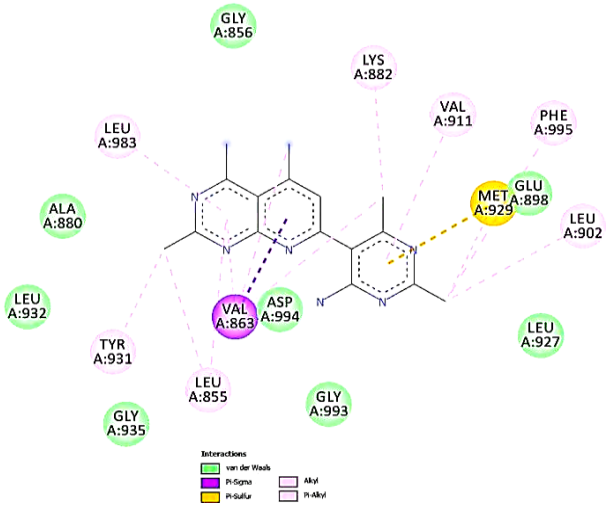


Figure 3: 2-D diagram of the top ligand attached to the JAK2 enzyme

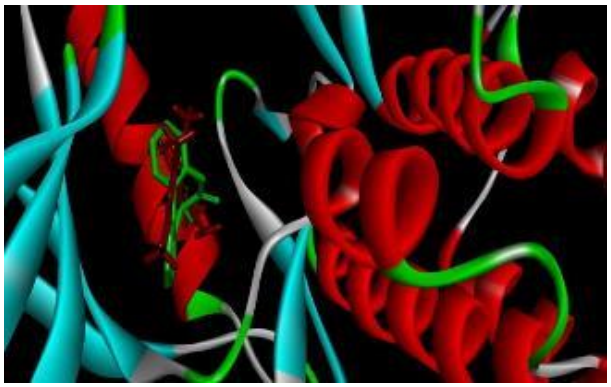


Figure 4: Molecular overlay representation of JAK2-top ligand complex compared to the 3JY9 reference crystal. The top ligand and reference ligand are shown as red and green stick models, respectively

ligand movement RMSD after superposition on the receptor, and ligand conformation RMSD after superposition on the ligand plotted against simulation time. For brevity, these plots were not included here. Figure 5 displays the solute RMSD from the starting structure plotted against simulation time.

The RMSD-time plot indicated that equilibrium was reached around 20 ns. Subsequently, the JAK2-top ligand complex remained stable. From 20 ns until the end of the simulation at 120 ns, backbone RMSD fluctuations were confined within a narrow range of 1.0 – 1.7 Å (Figure 5). Thus, the screening and molecular interaction data, pharmacokinetic features and simulation plots indicated that the reported ligand may be a promising lead against JAK2.

DISCUSSION

A new class of immunomodulatory drugs with notable impact on several cytokine signaling pathways is Janus kinase inhibitors (JAKis). They have changed the treatment scene for autoimmune diseases like rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. However, they have dual ability to control immunological reactions influencing pathogenic inflammation, and protective immunity [21]. Recent developments in computational modeling methods, including molecular docking, molecular dynamics (MD) simulations, have significantly accelerated the discovery and development of new JAK2 inhibitors by enabling rapid screening and optimization of possible compounds with high affinity and selectivity for JAK2 [22]. Therefore, this study was aimed at identifying a better lead molecule for the suppression of JAK2 through molecular docking, molecular dynamics simulation, and high-throughput screening.

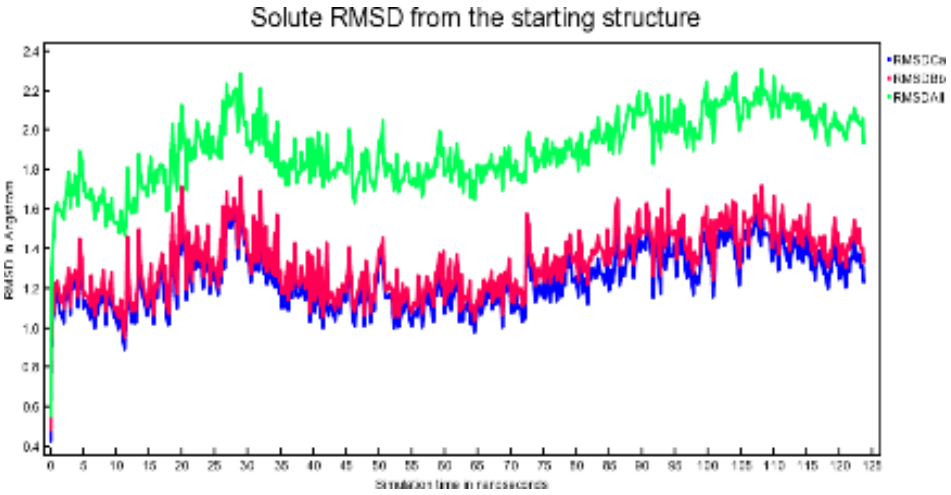


Figure 5: Root Mean Square Deviation (RMSD) of the solute from the initial structure over simulation time

The MCULE database was used to screen 5 million ligands in a structure-based manner. The ligand hits were prioritized based on their VINA scores relative to the 3JY9 domain in the active site [23,24]. Additional filtering was accomplished by methods such as the MCULE-Toxicity Checker, Zero-RO5-Violation-Check, synthetic accessibility assessment, and comprehensive pharmacokinetic characteristics. The top ligand was 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d) pyrimidin-7-yl) and demonstrated strong binding with JAK2 involving 17 amino acid residues in the active site pocket. This finding was in tandem with previous studies, which revealed that selected key amino acid residues from pharmacophore-based virtual screening were LYS905, GLU957, LEU959, and ASP1003 in JAK1; GLU930 and LEU932 in JAK2; and GLU905 and CYS909 in JAK3 [25].

Marine biomolecules, including Sargachromanol G, Isopseudopterosin E, Seco-Pseudopterosin, and CID 10071610, exhibited selective binding and significantly elevated binding energy to JAK1 active/potential sites compared to authorized inhibitors. However, Zoanthoxanthin and Fuscoside E interact with the essential residues of JAK2, GLU930, and LEU932. Furthermore, Phorbaketal and Fuscoside E seem to be promising candidates capable of inhibiting JAK3 activity by targeting the 3JY9 domain. The findings corroborated the inhibition of 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d) pyrimidin-7-yl) in the same amino acid residues in the same active site pocket. The RMSD-time graph demonstrated that equilibrium was attained at approximately 20 ns. Also, the JAK2-top ligand combination was stable. Between 20 ns and the conclusion of the simulation at 120 ns, the backbone RMSD variations were restricted to a small range of 1.0 – 1.7 Å.

The screening and molecular interaction data, pharmacokinetic characteristics, and simulation plots suggested that the disclosed ligand may be regarded as a potential candidate against JAK2. Vaziri-Amjad *et al* [26] employed the Discovery Studio Visualizer tool to clarify interactions between the highest-ranked JAK2 inhibitors and residues within the JAK2 ATP-binding site. The findings differed from the results of this present study in the same domain. Also, twelve flavonoids, two anthraquinones, and three cinnamic acids exhibited significant binding affinities to the protein kinase domain of the receptor, with a threshold of $\Delta G_{binding} < -10$ kcal/mol [26]. The docked conformations of orientin, pulmatin, and chlorogenic acid were stable throughout 60 ns of computational simulations. The computed average root mean square deviation values for JAK2 in complex with orientin, chlorogenic acid, and pulmatin were 2.04, 2.06, and 1.95 Å, respectively. This study, therefore, has revealed the need for the creation of innovative and efficacious pharmaceuticals for human JAK2 therapy as 4-pyrimidinamine, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d) pyrimidin-7-yl) component.

CONCLUSION

The ligand, 2,6-dimethyl-5-(2,4,5-trimethylpyrido (2,3-d)pyrimidin-7-yl)-4-pyrimidinamine, met the ADMET criteria and was confirmed through an extended molecular dynamics simulation lasting 120 ns. This ligand is a promising lead for designing inhibitors against JAK2 and should be further evaluated in wet laboratory experiments.

DECLARATIONS

Acknowledgement/funding

None.

Ethical approval

None required.

Use of Artificial intelligence/Large language models

We also declare that we did not use generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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