RESEARCH ARTICLE

In-silico Design and Development of Multi-Target Agents Targeting Glycogen Synthase Kinase-3 Beta and Vascular Endothelial Growth Factor Receptor 2 for Acute Myeloid Leukemia

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ABSTRACT

This research focuses on the *in-silico* design of multi-target agents for acute myeloid leukemia (AML), targeting GSK-3β and VEGFR2. Using TTD data, we selected a promising target pair and considered 20,818 agents. Ligand-based screening in ChEMBL identified compounds with diverse structures and favorable interactions. Protein structures (GSK-3β: PDB ID 1Q5K, VEGFR2: PDB ID 3QTK) underwent rigorous quality assessment, indicating high-quality models. Molecular docking revealed varied affinities, with CHEMBL183504 showing strong affinity for GSK-3β in pocket C1, and CHEMBL185922 for VEGFR2 in pocket 2. CHEMBL181959 exhibited dual affinity. Further experimental validation is needed. In conclusion, this study provides insights for AML therapy, guiding compound selection and structural quality assessment for potential drug development.

Keywords: Acute myeloid leukemia, Multi-target agents, Vascular endothelial growth factor receptor 2, Glycogen synthase kinase-3 beta, *In-silico* design, Ligand-based virtual screening.

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INTRODUCTION

Acute myeloid leukemia (AML) stands as a formidable challenge within the landscape of hematologic malignancies, demanding innovative therapeutic strategies to improve patient outcomes.[1] The intricate molecular landscape of AML involves dysregulation in key signaling pathways, necessitating the identification of precise molecular targets for therapeutic intervention. Two such targets, glycogen synthase kinase-3 beta (GSK-3β) and vascular endothelial growth factor receptor 2 (VEGFR2), have occurred as crucial players in the orchestration of cellular processes integral to leukemic progression. The intricate interplay between these targets and their modulation of pathways pivotal to AML pathophysiology underscore their significance in the pursuit of targeted therapies.[2]

GSK-3β, involved in a wide range of biological activities, including cell proliferation, differentiation, and cell death, is a complex serine/threonine kinase. Its aberrant activation has been linked to leukemogenesis, making it an attractive therapeutic target in the context of AML. Similarly, VEGFR2, a key player in angiogenesis, has been implicated in the sustenance of leukemic microenvironments. Targeting both GSK-3β and VEGFR2 simultaneously presents an intriguing avenue for disrupting multiple facets of AML pathogenesis.[3]

In the realm of precision medicine, *in-silico* approaches offer a powerful means to navigate the vast chemical space and identify potential multi-target agents. The computational design and development of compounds with the ability to modulate both GSK-3β and VEGFR2 present a novel and rational strategy for therapeutic intervention in AML. Such

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an approach holds promise for enhancing treatment efficacy while mitigating potential off-target effects associated with traditional single-target therapies.

Central to our research is the inclusion of cyclopropane-carboxylic acid [6-(4-Fluoro-Phenyl)-Furo[2,3-d]Pyrimidin-4-yl]-Amide, a multi-target agent identified through an exhaustive exploration of the therapeutic target database. This compound, with its exclusive structural features, serves as a cornerstone in our endeavor to bridge the gap between computational design and experimental validation.[4]

In this comprehensive study, we embark on an in-depth exploration of the structural and functional aspects of GSK-3β and VEGFR2, employing advanced *in-silico* methodologies. The integration of ligand-based virtual screening, molecular docking simulations, and lead optimization processes aims to identify compounds with optimal binding affinities and pharmacokinetic profiles.

This research marks a critical step towards the prospect of personalized and effective therapeutic interventions for AML. By amalgamating cutting-edge computational techniques with an understanding of the intricate molecular dynamics of AML, we envision a paradigm shift in the management of this complex hematologic disorder. Our pursuit is anchored in the belief that this *in-silico* design and development of multi-target agents will contribute significantly to the evolving landscape of targeted therapies, paving the way for more effective and tailored treatments for AML patients.

MATERIALS AND METHODS

Selection of Therapeutic Targets

Utilizing the therapeutic target database (TTD), we meticulously identified crucial therapeutic targets central to our study: GSK-3β and VEGFR2. These selections were grounded in their pivotal roles within the context of AML. Employing focused queries and filters within TTD, our selection of potential multi-target agents was refined based on criteria such as disease relevance and biological pathways pertinent to AML. Detailed information on the selected targets, including their functions and associated drugs or ligands, was meticulously retrieved. The integration of the multi-target agent cyclopropanecarboxylic acid [6-(4-Fluoro-Phenyl)-Furo[2,3-d]Pyrimidin-4-yl]-Amide, identified through our database exploration, enriched our study.[5,6]

Ligand-based Virtual Screening

The Swiss Similarity online tool was utilized to do ligand-based virtual screening. Query molecule, cyclopropanecarboxylic acid [6-(4-Fluoro-Phenyl)-Furo[2,3-d]Pyrimidin-4-yl]-Amide in SMILES format, was juxtaposed against a screening database comprising licensed medications, bioactive materials, and an additional 200 million virtual compounds from ChEMBL (version 29) using bioactive and extended connectivity circular fingerprint.[7,8]

Protein Structure Pre-processing and Quality Assessment for docking studies

The three-dimensional structures of GSK-3β (PDB ID: 1Q5K) and VEGFR2 (PDB ID: 3QTK) were acquired from the protein data bank (PDB). Rigorous pre-processing involved energy minimization, hydrogen atom addition, and water molecule removal. Quality assessment included analysis using the VADAR 1.8 server for geometric and structural parameters, as well as validation through the MolProbity server for geometry, clash scores, and other critical structural parameters.[9,10]

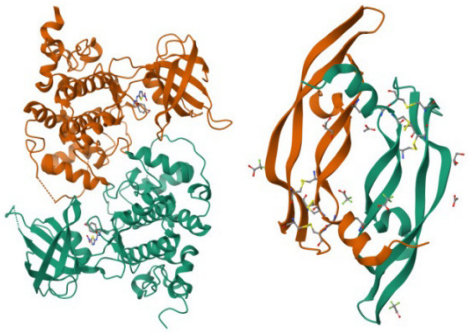


Figure 1: GSK-3β (PDB ID: 1Q5K) and VEGFR2 (PDB ID: 3QTK)

Molecular Docking Simulations

Investigating the interaction of the top 10 compounds selected from ligand-based screening with GSK-3β (PDB ID: 1Q5K) and VEGFR2 (PDB ID: 3QTK) was accomplished through molecular docking simulations (Figure 1). By using cavity detection as guidance, the CB-Dock tool made it easier to determine the docking center, perform molecular docking simulations, and evaluate binding poses using docking scores in order to identify the most energetically advantageous binding conformations.[11]

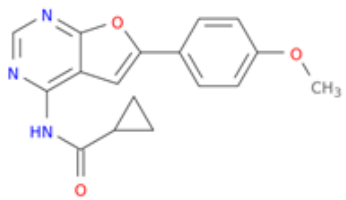
Lead Optimization

Subsequent to molecular docking, the physicochemical and pharmacokinetic properties of the lead compound were scrutinized using(https://admetmesh.scbdd.com/service/evaluation/cal) ADMETlab 2.0 server, offering invaluable insights into the compound's ADMET profile, ensuring a comprehensive understanding of its potential as a therapeutic candidate (Figure 2).[12]

RESULTS

Results of Selection of Therapeutic Targets

TTD Version 6.1.01 revealed the composition and effectiveness of 20,818 multitarget agents against 385 target pairings (Table 1). From this GSK-3β and VEGFR2)pair was selected. These selections were grounded in their pivotal roles within the context of AML.



COC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CC3)N=CN=C2O1

Figure 2: 2D Structure and SMILES of lead molecule

Table 1: Multi-target agents from TTD version 6.1.01

Target pair	*Drug name*
GSK-VEGFR	Cyclopropanecarboxylic acid [6-(4-fluoro-phenyl)-furo[2,3-d]pyrimidin-4-yl]-amide
GSK-VEGFR	2-Cyclopentyl-N-[6-(4-methoxy-phenyl)-furo[2,3-d]pyrimidin-4-yl]-acetamide
GSK-VEGFR	Cyclopropanecarboxylic acid [6-(4-methoxy-phenyl)-furo[2,3-d]pyrimidin-4-yl]-amide
GSK-VEGFR	Pyrrolidine-1-carboxylic acid [6-(4-methoxy-phenyl)-furo[2,3-d]pyrimidin-4-yl]-amide
GSK-VEGFR	Cyclopropanecarboxylic acid [6-(4-chloro-phenyl)-furo[2,3-d]pyrimidin-4-yl]-amide
GSK-VEGFR	4-amino-5-(4-(benzenesulfonylamino)-phenyl)-6-(3-pyridyl)-furo[2,3-d]pyrimidine
GSK-VEGFR	Cyclopropanecarboxylic acid (6-phenyl-furo[2,3-d]pyrimidin-4-yl)-amide
GSK-VEGFR	SID124349991

Table 2: Ligand-Based Virtual screening by Swiss similarity

CHEMBL ID	*Bioactivity score*	*Chemical structure*
CHEMBL362030	1.000	COC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CC3)N=CN=C2O1
CHEMBL183504	1.000	FC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CC3)N=CN=C2O1
CHEMBL182283	0.839	CC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CC3)N=CN=C2O1
CHEMBL182904	0.839	ClC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CC3)N=CN=C2O1
CHEMBL181147	0.766	COC1=CC=C(C=C1)C1=CC2=C(NC(=O)N3CCOCC3)N=CN=C2O1
CHEMBL181856	0.753	COC1=CC=C(C=C1)C1=CC2=C(NC(=O)N3CCCC3)N=CN=C2O1
CHEMBL183077	0.723	COC1=CC=C(C=C1)C1=CC2=C(NC(=O)C(C)C)N=CN=C2O1
CHEMBL360534	0.640	O=C(NC1=C2C=C(OC2=NC=N1)C1=CC=CC=C1)C1CC1
CHEMBL182560	0.635	COC1=CC=C(C=C1)C1=CC2=C(NC(=O)CCSC)N=CN=C2O1
CHEMBL185922	0.543	FC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CCCC3)N=CN=C2O1
CHEMBL181959	0.543	COC1=CC=C(C=C1)C1=CC2=C(NC(=O)C3CCCC3)N=CN=C2O1

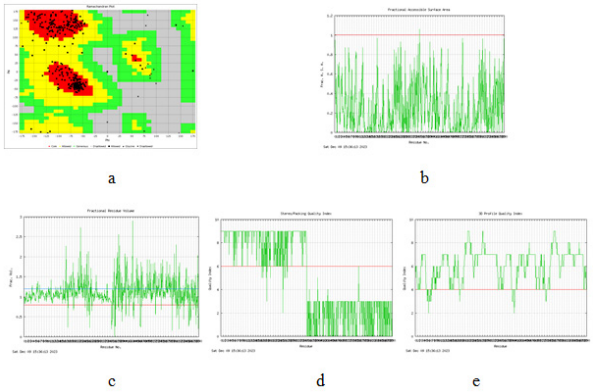


Figure 3: (a) Ramachandran plot. (b) Fractional accessible surface area (c) Fractional residue volume (d) Stereo/Packing quality index (e) 3D profile quality index of GSK-3β

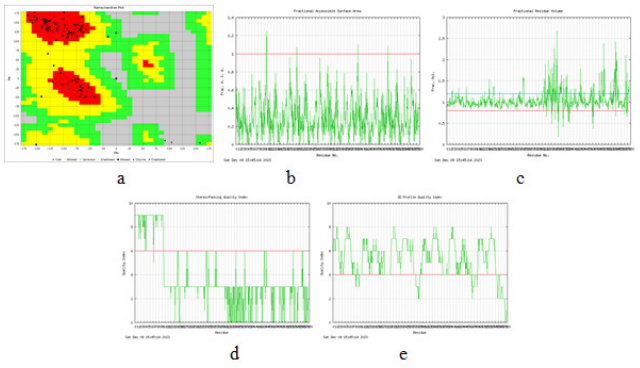


Figure 4: (a) Ramachandran plot. (b) Fractional accessible surface area (c) Fractional residue volume (d) Stereo/Packing quality index (e) 3D profile quality index of VEGFR2

Ligand-Based Virtual Screening

The Swiss similarity virtual screening identified several promising candidate ligands for the target protein. CHEMBL362030 and CHEMBL183504 emerged as top contenders with the highest binding potential. Other similar compounds like CHEMBL182283 and CHEMBL182904 showed comparable promise, while slight variations like chlorination in CHEMBL182904 or substitutions on the N3 atom in others like CHEMBL181147 and CHEMBL181856 led to decreased bioactivity scores. Interestingly, the presence of sulfur in CHEMBL182560 further lowered its binding potential. Overall, this data highlights the potential of several identified compounds for further development as ligands for the target protein, warranting further investigation.

Results of Protein Structure Pre-Processing and Quality Assessment for Docking Studies

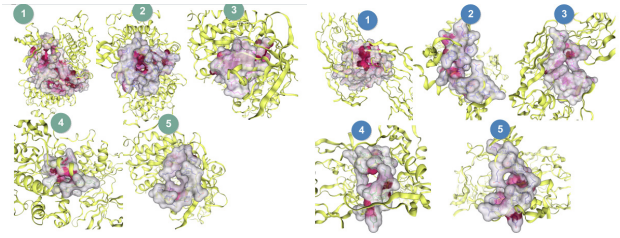
The analysis of the Ramachandran plot for GSK-3β (PDB ID: 1Q5K) and VEGFR2 (PDB ID: 3QTK) revealed well-behaved backbone dihedral angles with minimal outliers, indicating a

high quality of stereochemistry in both structures (Figures 3 and 4). The fractional accessible surface area showed variations, suggesting differential solvent accessibility and potential implications for ligand binding. Fractional residue volume indicates tightly packed residues, contributing to the stability of the protein structures. The stereo/packing quality index highlighted favorable atomic packing, reinforcing the overall structural integrity. The 3D profile quality index confirmed the reliability of the three-dimensional structures. These analyses collectively provide valuable insights into the quality, stability, and functional implications of GSK-3β and VEGFR2, crucial for understanding their roles in cellular processes and potential therapeutic targeting (Table 2).

The biomolecular model exhibits generally satisfactory structural characteristics, with low percentages of poor rotamers (1.95%) and Ramachandran outliers (1.48%). The absence of Cβ deviations, bad bonds, and low numbers of bad angles (0.03%) and cisprolines (0.00%) reflects high-quality bond and angle geometry. However, improvements are suggested in achieving a higher percentage of favored rotamers (96.25%) and reducing CaBLAM outliers (2.0%) to meet more stringent criteria. The Rama distribution Z-score (-1.48 ± 0.30) falls within an acceptable range, indicating a reasonable Ramachandran distribution. Attention to specific areas for refinement is recommended to enhance the overall quality of the biomolecular model (Table 3).

Results of Molecular Docking Simulations

The compounds show diverse binding affinities, as indicated by their docking scores in different pockets. Notably, CHEMBL183504 demonstrates a strong binding affinity with a score of -8.0 in pocket C1, involving interactions with chains C, E, and F. Additionally, CHEMBL181856 and CHEMBL181959 exhibit favorable scores of -8.3, with interactions in pockets C2 and C1, respectively. However, some compounds, such as CHEMBL362030 and CHEMBL182283, have slightly lower scores of -7.6 and -7.7 in pocket C2. Overall, these findings suggest that certain compounds may be more potent inhibitors of GSK-3β, warranting further investigation and potential optimization for drug development. It is essential to consider not only the docking scores but also the specific interacting residues in each pocket for a comprehensive understanding of the binding interactions (Figures 5-7).



a b

Figure 5: Cavities detected in a) GSK-3β b) VEGFR 2 by CB-dock server

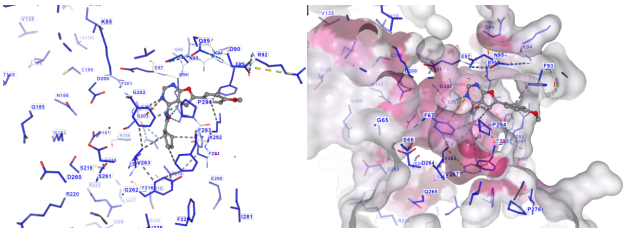


Figure 6: Interaction between GSK-3β and lead CHEMBL181959

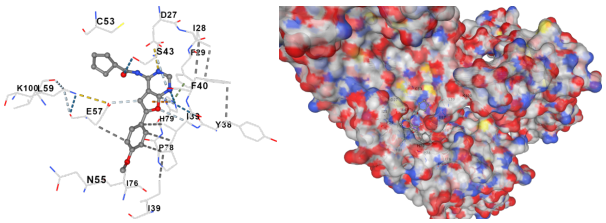


Figure 7: Interaction between GSK-3β and lead CHEMBL181959

Notably, CHEMBL185922 stands out with an exceptionally high docking score of -9.7 in pocket 2, demonstrating a strong binding affinity with interacting residues in chains A and B. Similarly, CHEMBL183504, CHEMBL182904, and CHEMBL181147 also exhibit potent binding with scores of -9.4, -9.0, and -9.3, respectively, in pocket 2. However, some

Table 3: Summary statistics of structure validation by MolProbityserver

	Poor rotamers	12	1.95%	Goal: <0.3%
Protein geometry	Favored rotamers	591	96.25%	Goal: >98%
	Ramachandran outliers	10	1.48%	Goal: <0.05%
	Ramachandran favored	634	93.65%	Goal: >98%
	Rama distribution Z-score	-1.48 ± 0.30		Goal: abs(Z score) < 2
	Cβ deviations >0.25Å	0	0.00%	Goal: 0
	Bad bonds:	0/5695	0.00%	Goal: 0%
	Bad angles:	2/7739	0.03%	Goal: <0.1%
Peptide Omegas	CisProlines:	0/54	0.00%	Expected: ≤1 per chain, or ≤5%
Low-resolution Criteria	CaBLAM outliers	13	2.0%	Goal: <1.0%
	CA Geometry outliers	3	0.45%	Goal: <0.5%
Additional validations	Chiral volume outliers	0/865		

Table 4: Molecular docking simulations results

CHEMBL ID	*Pocket, Score and Interactions of GSK-3β*	*Pocket, Score and Interactions of VEGFR2*
CHEMBL362030	Pocket: C2 & Score: -7.6 Chain E: GLY52 CYS53 CYS54 ASN55 ASP56 GLU57 LEU59 GLU60 LYS100 Chain F: ASP27 PHE29 GLU35 ILE36 TYR38 ILE39 PHE40 SER43 CYS44	Pocket: 2 & Score: -8.5 Chain A: PHE67 GLN89 ASP90 ARG92 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 ALA204 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PHE293 PRO294
CHEMBL183504	Pocket: C1 & Score: -8.0 Chain C: ILE39 ILE76 PRO78 HIS79 Chain E: ASP27 ILE28 PHE29 TYR38 ILE39 PHE40 SER43 Chain F: GLU57 LYS100	Pocket: 2 & Score: -9.4 Chain A: PHE67 VAL87 GLN89 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 PHE201 GLY202 SER203 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PRO294
CHEMBL182283	Pocket: C2 & Score: -7.7 Chain E: GLY52 CYS53 CYS54 ASN55 ASP56 GLU57 LEU59 LYS100 Chain F: VAL26 ASP27 PHE29 GLU35 TYR38 ILE39 PHE40 SER43 CYS44	Pocket: 2 & Score: -8.5 Chain A: PHE67 GLN89 ASP90 ARG92 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 ALA204 Chain B: VAL263 PHE291 LYS292 PHE293 PRO294
CHEMBL182904	Pocket: C3 & Score: -7.6 Chain A: ASP27 PHE29 ILE36 ILE39 PHE40 LYS41 SER43 Chain D: CYS53 CYS54 ASN55 ASP56 GLU57 GLY58 LEU59 GLU60 LYS100 Chain F: ARG98 PRO99 LYS101	Pocket: 2 & Score: -9.0 Chain A: PHE67 GLN89 ASP90 ARG92 PHE93 LYS94 ARG96 GLU97 ARG180 GLY202 SER203 ALA204 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PHE293 PRO294
CHEMBL181147	Pocket: C3 & Score: -7.6 Chain A: ASP27 PHE29 ILE36 ILE39 PHE40 LYS41 SER43 Chain D: CYS53 CYS54 ASN55 ASP56 GLU57 GLY58 LEU59 GLU60 LYS100 Chain F: ARG98 PRO99 LYS101	Pocket: 2 & Score: -9.3 Chain A: PHE67 GLN89 ASP90 ARG92 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PHE293 PRO294
CHEMBL181856	Pocket: C2 & Score: -8.3 Chain E: GLY52 CYS53 CYS54 ASN55 ASP56 GLU57 LEU59 LYS100 Chain F: LEU25 VAL26 ASP27 PHE29 GLU35 ILE36 TYR38 ILE39 PHE40 SER43 CYS44	Pocket: 2 & Score: -8.8 Chain A: PHE67 VAL87 LEU88 ASP90 ARG92 PHE93 ASN95 ARG96 GLU97 PHE201 GLY202 SER203 Chain B: LYS292 PHE293 PRO294
CHEMBL183077	Pocket: C2 & Score: -7.5 Chain E: GLY52 CYS53 CYS54 ASN55 ASP56 GLU57 LEU59 Chain F: LEU25 VAL26 ASP27 PHE29 GLU35 ILE36 TYR38 ILE39 PHE40 SER43 CYS44	Pocket: 2 & Score: -8.7 Chain A: PHE67 VAL87 LEU88 GLN89 ASP90 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PHE293 PRO294
CHEMBL360534	Pocket: C1 & Score: -7.4 Chain C: ILE39 ILE76 PRO78 HIS79 Chain E: ASP27 ILE28 PHE29 TYR38 ILE39 PHE40 SER43 Chain F: GLU57	Pocket: 2 & Score: -8.8 Chain A: PHE67 LYS85 VAL87 LEU88 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 ALA204 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PHE293 PRO29
CHEMBL182560	Pocket: C2 & Score: -7.2 Chain E: GLY52 CYS53 CYS54 ASN55 ASP56 GLU57 LEU59 LYS100 Chain F: LEU25 VAL26 ASP27 PHE29 GLU35 ILE36 TYR38 ILE39 PHE40 SER43 CYS44	Pocket: 2 & Score: -7.6 Chain A: PHE67 GLN89 ASP90 ARG92 PHE93 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 ALA204 VAL214 TYR216 ILE217 Chain B: VAL263 LYS292 PHE293 PRO294
CHEMBL185922	Pocket: C2 & Score: -7.9 Chain E: GLY52 CYS53 CYS54 ASN55 ASP56 GLU57 LEU59 Chain F: LEU25 VAL26 ASP27 PHE29 GLN30 GLU35 TYR38 ILE39 PHE40 SER43 CYS44	Pocket: 2 & Score: -9.7 Chain A: PHE67 LYS85 VAL87 GLN89 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 GLY202 VAL214 TYR216 ILE217 Chain B: VAL263 PHE291 LYS292 PRO294
CHEMBL181959	Pocket: C1 & Score: -8.3 Chain B: ASN55 Chain C: ILE39 ILE76 PRO78 HIS79 Chain E: ASP27 ILE28 PHE29 TYR38 ILE39 PHE40 SER43 Chain F: CYS53 GLU57 LEU59 LYS100	Pocket: 2 & Score: -9.3 Chain A: PHE67 GLN89 ASP90 ARG92 PHE93 LYS94 ASN95 ARG96 GLU97 ARG180 GLY202 SER203 ALA204 VAL214 TYR216 Chain B: VAL263 PHE291 LYS292 PHE293 PRO294

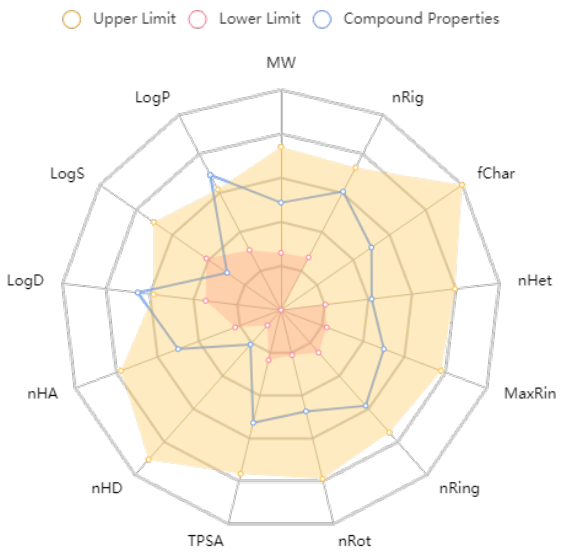


Figure 8: Optimization of CHEMBL181959

compounds, such as CHEMBL182560, display a lower score of -7.6, suggesting a comparatively weaker binding affinity. Overall, these findings indicate that certain compounds possess significant potential as inhibitors for VEGFR2, warranting further investigation and consideration for drug development. The choice of lead compounds should consider both the docking scores and the specific interacting residues in pocket 2 for a comprehensive assessment of their binding interactions and potential therapeutic efficacy.

A combined analysis of the data reveals that CHEMBL181959 is a compound that stands out as it demonstrates strong binding affinity for both GSK-3β and VEGFR2. In GSK-3β, it achieves a notable score of -8.3 in pocket C1 with interactions in chains B, C, E, and F. Simultaneously, in VEGFR2, it exhibits a high docking score of -9.3 in pocket 2 with interactions in chains A and B. This suggests that CHEMBL181959 has the potential to be a multitarget agent (Figure 8), showing significant binding affinity for both GSK-3β and VEGFR2. Further investigation and experimental validation are warranted to confirm the dual inhibitory activity and to explore the therapeutic implications of this compound in targeting both GSK-3β and VEGFR2, which could be valuable for diseases or conditions where these targets play a role (Table 4).

The medicinal chemistry profile of the compound is generally favorable, with a high QED (Quantitative Estimate of Drug-likeness) of 0.778, good synthetic accessibility (SA score of 2.317), and adherence to Lipinski, Pfizer, GSK, and Golden Triangle rules, indicating its potential as a drug candidate. However, some alerts in the ALARM NMR rule warrant cautious consideration. In terms of ADME properties, the compound shows poor $CaCO^{-2}$ permeability, suggesting limited absorption, but favorable MDCK permeability. The compound is a P-glycoprotein (Pgp) inhibitor and demonstrates significant BBB penetration, indicating potential central nervous system activity. Distribution characteristics reveal high plasma protein binding and low unbound fraction, suggesting limited distribution in the unbound form. The compound exhibits strong inhibitory effects on various cytochrome P450 (CYP) isoforms, which may impact its metabolism. Overall, the compound possesses both promising drug-like properties and potential challenges, emphasizing the need for further optimization and in-depth preclinical investigations.

CONCLUSION

This research endeavors to address the pressing need for innovative therapeutic strategies in the realm of AML through *in-silico* design and development of multi-target agents targeting GSK-3β and VEGFR2. By leveraging the wealth of information from TTD and ChEMBL, a meticulous selection process identified a potent target pair, laying the foundation for subsequent investigations.

The ligand-based virtual screening unveiled a diverse set of compounds with substantial bioactivity scores, showcasing their potential as promising candidates for AML treatment. This diversity in chemical structures opens avenues for optimization and further exploration in the drug development pipeline.

Protein structure pre-processing and quality assessments ensured the reliability of the biomolecular models for GSK-3β and VEGFR2. The detailed analyses, including Ramachandran plots and various quality indices, provided a comprehensive understanding of the structural integrity, stability, and functional implications of these vital targets. These structural insights are pivotal for rational drug design and optimization.

Molecular docking studies illuminated the binding affinities of selected compounds, revealing distinct interactions within different pockets of GSK-3β and VEGFR2. Notably, compounds such as CHEMBL183504 and CHEMBL185922 exhibited remarkable affinities, signifying their potential as lead candidates for further scrutiny.

Intriguingly, CHEMBL181959 emerged as a compound with significant binding affinity for both GSK-3β and VEGFR2, suggesting its potential as a multitarget agent. This discovery prompts further experimental validation to ascertain its dual inhibitory activity and evaluate its therapeutic implications, potentially revolutionizing AML treatment strategies.

In conclusion, this *in-silico* study provides a comprehensive and systematic approach to the design and development of multi-target agents for AML therapy. The amalgamation of computational analyses, structural assessments, and molecular docking studies has yielded valuable insights, paving the way for subsequent experimental validations and optimization of lead compounds. As we embark on the journey from *in-silico* predictions to experimental validations, the findings presented herein contribute significantly to the ongoing pursuit of effective therapeutic interventions for Acute Myeloid Leukemia.

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