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Molecular Docking and Drug-Likeness Assessment of Novel MCL-1 Modulators as Promising Candidates for Breast Cancer Treatment

AHMED NOURI A LSHARKSI [1*]

[1] Department of Nursing, Higher Institute of Sciences and Technology, Tawergha, Libya [1]

email; ahmedalsherkas87@gmail.com

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ABSTRACT

Breast cancer remains a major global health challenge, with the dysregulation of intrinsic apoptotic pathways playing a pivotal role in its progression and therapeutic resistance. Myeloid cell leukemia 1 (MCL-1), an anti-apoptotic protein of the BCL-2 family, represents a key target for rational chemical design and drug discovery. In this study, a computational chemistry and cheminformatics approach was employed to evaluate selected Pinaceae-derived phytochemicals as potential chemical leads against the MCL-1 structure (PDB ID: 5FDR). Molecular docking simulations were conducted to characterize the structural binding affinities, molecular orientations, and specific chemical interactions (e.g., hydrogen bonding and hydrophobic contacts) within the MCL-1 active site. Furthermore, the compounds were evaluated for their physicochemical drug-likeness profiles and predicted pharmacokinetic properties. Among the screened phytochemicals, IMPHY000001 (Matairesinol), IMPHY003007 (Dihydrodehydrodiconiferyl alcohol), and IMPHY012983 ((7R)-7-Hydroxylariciresinol) demonstrated superior computational binding energy profiles and key non-covalent interactions with critical active-site residues. These compounds also exhibited favorable chemical drug-likeness parameters, highlighting their potential as viable chemical scaffolds. Overall, this computational study delineates the structural and chemical binding characteristics of these Pinaceae derivatives, providing a theoretical chemical framework for future synthetic optimization and subsequent experimental biological validation.

Keywords: Breast cancer, MCL-1 inhibitors, Computational chemistry, Molecular docking, Cheminformatics, Pinaceae family, Phytochemicals.

INTRODUCTION

Breast cancer is a highly heterogeneous malignancy characterized by the uncontrolled proliferation of mammary epithelial cells and remains a leading cause of cancer-related mortality worldwide (World Health Organization, WHO 2022). Global estimates indicate that breast cancer accounted for approximately 670,000 deaths in 2022 and has surpassed lung cancer as the most frequently diagnosed cancer globally (Siegel et al., 2022). A critical impediment in clinical management is therapeutic resistance, which is frequently mediated by the evasion of programmed cell death (Bock and Tait, 2020). The intrinsic apoptotic pathway, tightly regulated by the B-cell lymphoma-2 (BCL-2) family of proteins, serves as a primary checkpoint in this mechanism (Deng et al., 2024). Among these proteins, Myeloid Cell Leukemia-1 (MCL-1) acts as a crucial anti-apoptotic factor, sequestering pro-apoptotic BH3-only proteins and preventing cell death initiation (Wang et al., 2021).

Overexpression of MCL-1 is extensively documented in breast carcinomas and strongly correlates with disease recurrence, metastatic capability, and chemoresistance to conventional treatments, including taxanes, anthracyclines, and early-generation BH3 mimetics (Bolomsky et al., 2020; Pervushin et al., 2020; Deng et al., 2024). Consequently, the chemical inhibition of MCL-1 using small-molecule modulators represents an attractive strategy to restore apoptotic signaling and resensitize resistant cancer cells.

Modern drug discovery relies increasingly on computational chemistry, computer-aided drug design (CADD), and cheminformatics to accelerate the identification and structural optimization of novel chemical entities (Turabi et al., 2023). In silico strategies—such as molecular docking, binding free-energy estimations, and molecular dynamics—provide detailed structural and thermodynamic insights into chemical ligand–protein interactions prior to laboratory synthesis and biological evaluation. These computational methods facilitate the high-throughput screening of diverse chemical libraries, allowing for the precise analysis of non-covalent binding forces, steric fit, and physicochemical properties, thereby significantly optimizing resource allocation in early-stage drug development (Turabi et al., 2023).

Rather than relying on direct biological assaying, the primary objective of this study is to perform a rigorous computational chemistry investigation evaluating Pinaceae-derived phytochemicals as potential small-molecule modulators of MCL-1 (PDB ID: 5FDR). Through molecular docking assessments, 2D/3D chemical interaction mapping, and in silico drug-likeness profiling, this study identifies promising chemical lead structures that warrant future experimental synthesis and biological validation.

2. Materials and methods

2.1 Protein retrieval

The three-dimensional structure of the human Myeloid Cell Leukemia-1 (MCL-1) protein was retrieved from the Protein Data Bank (PDB) under the accession code 5FDR. The selected structure has a reported resolution of 2.60 Å and contains MCL-1 in complex with a small-molecule inhibitor. The crystal structure was used as the target receptor for the subsequent molecular docking analysis. Before docking, the receptor structure and its associated ligand(s) were inspected to identify the protein chains, residue numbering, and ligand-binding region. The receptor preparation and docking parameters were subsequently defined using Molegro Virtual Docker (MVD) version 6.0 (2013).

3. Results and Discussion

The present study employed a computational molecular docking approach to identify phytochemicals from the Pinaceae family with potential to interact with the anti-apoptotic protein MCL-1. The molecular docking results provided information on the predicted binding poses, docking scores, and ligand–residue interactions within the MCL-1 binding region. Among the screened compounds, IMPHY000001, IMPHY003007, and IMPHY012983 were prioritized based on their favorable MolDock scores and their predicted interactions with residues located within the MCL-1 binding site. These interactions included hydrogen bonding, hydrophobic contacts, and aromatic interactions, which may contribute to the predicted accommodation of the ligands within the binding region. However, the docking scores represent computational predictions rather than experimentally determined binding affinities, and the observed interactions should therefore be interpreted as preliminary evidence supporting further investigation of these compounds as potential MCL-1 inhibitor candidates.

This agrees with earlier studies showing that MCL-1 suppression or inhibition can restore apoptotic signaling and sensitize cancer cells to therapeutic agents (Pervushin et al., 2020; Deng et al., 2024; Zha et al., 2024).

3.1. Energy minimized after docking

Among the evaluated compounds, IMPHY002255 exhibited the most negative MolDock Score (−144.272), indicating a more favorable predicted docking score within the applied scoring function. However, its relatively high molecular weight (582.554 g/mol) and multiple violations of Lipinski's rule of five may limit its drug-likeness and potential pharmacokinetic suitability. In contrast, IMPHY000001, IMPHY003007, and IMPHY012983 showed favorable MolDock Scores of −132.517, −121.381, and −126.318, respectively, while also satisfying the evaluated Lipinski drug-likeness criteria. Therefore, these three compounds were prioritized as promising computational candidates based on the combined consideration of their predicted docking scores and drug-likeness characteristics. It should be noted that MolDock Scores are computational scoring values and should

not be interpreted as experimentally determined binding affinities. The complete docking results are presented in Table 3.1.

Table 3.1: docking analysis of ligands using Molecular Virtual Docker

compound ID	MolDock Score	Rerank Score	RMSD	HBond	MW (g/mol)
IMPHY000001	132.517−	102.686−	N/A	2.979−	359.393
IMPHY000184	120.390−	64.455−	N/A	2.500−	451.661
IMPHY002255	144.272−	106.790−	N/A	12.445−	582.554
IMPHY003007	121.381−	95.458−	N/A	7.520−	360.401
IMPHY003992	126.169−	119.302−	N/A	20.249−	611.568
IMPHY004631	126.233−	97.237−	N/A	2.389−	283.469
IMPHY006558	125.919−	33.542−	N/A	2.500−	438.813
IMPHY012983	126.318−	32.104−	N/A	11.664−	376.400
IMPHY014990	124.141−	92.968−	N/A	1.499−	279.438
IMPHY015054	121.104−	91.638−	N/A	18.465−	449.385

* **RMSD values were not available from the original docking output and therefore could not be independently verified.**

The binding interaction analysis revealed recurring contacts involving His252, Asn223, Arg263, Thr226, and Glu225. These residues are located within or near the MCL-1 binding region involved in interactions with BH3-only proteins such as BIM and BAK. The predicted occupancy of this region by the selected phytochemicals may indicate a potential for interference with protein–protein interactions; however, such an effect cannot be established from molecular docking alone. Among the selected compounds, IMPHY012983 exhibited a relatively extensive network of predicted hydrogen bonds and aromatic interactions involving Phe270, suggesting favorable ligand–site complementarity. These structural features may contribute to its favorable docking profile and support its prioritization for further investigation. The detailed interaction patterns are presented in Table 3.2.

Table 3.2. Identification of the phytochemicals by IMPPAT ID and chemical names

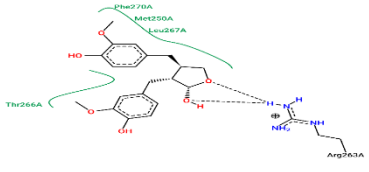
No.	IMPPAT Compound ID	Chemical name
1	IMPHY000001	Matairesinol
2	IMPHY000184	Pindrolactone
3	IMPHY002255	Abiesin
4	IMPHY003007	Dihydrodehydrodiconiferyl alcohol
5	IMPHY003992	Hesperidin
6	IMPHY004631	Stearic acid
7	IMPHY006558	1-Triacontanol
8	IMPHY012983	(7R)-7-Hydroxylariciresinol
9	IMPHY014990	Linoleic acid
10	IMPHY015054	Quercitrin

Table 3.3: The binding interaction mechanisms of the top hits inhibitors with the target compound

Ligand ID	Hydrogen Bonds	Steric Interactions
IMPHY000001	Arg 263 (A)	Thr 266 (A), Met 250 (A), Leu 267 (A), Phe 270 (A)
IMPHY000184	Thr 266 (A)	His 244 (A), Ala 227 (A), Thr 266 (A), Phe 228 (A), Met 231 (A), Met 250 (A), Phe 270 (A)
IMPHY002255	Asp 256 (C), Val 253 (C), His 252 (C), Asn 223 (A), His 224 (A), Thr 226 (B)	Thr 226 (A), Asp 256 (C), Val 253 (C), Lys 234 (B), Glu 225 (A), Met 231 (B), His 252 (C), Asn 223 (A), His 224 (A), Thr 226 (B)
IMPHY003007	Lys 234 (B), Asp 256 (C), Thr 226 (A)	His 252 (C), Val 253 (C), Asp 256 (C)
IMPHY003992	Gly 257 (C), Asn 223 (A), His 252 (C), Thr 226 (B), Val 253 (C), Asp 256 (C), Glu 225 (A), Thr 226 (A), Ala 227 (A)	Gly 257 (C), Asn 223 (A), His 252 (C), Gly 230 (B), Thr 226 (B), Asp 256 (C), Val 253 (C), Ala 227 (A), Thr 226 (A), Glu 225 (A)
IMPHY004631	Asn 223 (A)	Asn 223 (A)
IMPHY006558	Thr 259 (C)	Thr 259 (C), Asp 256 (D), Met 231 (A), Ala 227 (A), Gly 257 (C)
IMPHY012983	Lys 234 (B), Thr 226 (A), Glu 225 (A), Arg 222 (A), Asn 223 (A), His 252 (B)	Asn 223 (A), Asp 256 (C)
IMPHY014990	Arg 263 (A)	Arg 263 (A)
IMPHY015054	Asp 256 (B), His 252 (B), Thr 226 (A), Asn 223 (A), Arg 222 (A), Glu 225 (A), His 252 (C), Lys 234 (B)	His 252 (B), His 252 (C), Lys 234 (B), Arg 222 (A), Thr 226 (A), Asp 256 (C), Asn 223 (A)

The ProteinPlus server's PoseView-generated 2D interaction diagrams show the interactions between a few chosen phytochemicals from the Pinaceae family and the MCL-1 protein (PDB ID: 5FDR). By emphasizing the residues involved in hydrogen bonding, hydrophobic contacts, and aromatic stacking within the BH3-binding groove of MCL-1, these diagrams shed light on the molecular basis of inhibition.

1. IMPHY000001 (Matairesinol)–MCL-1 Complex (Figure 1)



w analysis showed multiple predicted hydrogen-bond
Gln211, together with hydrophobic contacts involving
romatic interaction with Phe270 was also observed. The
phobic, and aromatic contacts indicates that
in the MCL-1 binding region and may contribute to its
s provide structural support for considering Matairesinol as
ever, the predicted interactions should be interpreted as
nselves establish binding affinity or biological inhibition.

Figure 3.1: Poseview 2D molecular interaction diagram of IMPHY000001 (Matairesinol) and MCL-1 protein

2. IMPHY003007 (Dihydrodehydrodiconiferyl Alcohol)–MCL-1 Complex (Figure 2)

IMPHY003007 (Dihydrodehydrodiconiferyl alcohol), the PoseView analysis revealed several predicted polar interactions, including hydrogen bonds with Asn260, Ser245, and Arg263. Additional weaker hydrophobic or van der Waals contacts were predicted with residues such as Leu246 and Met231. These interactions indicate that IMPHY003007 can adopt a favorable orientation within the MCL-1 binding region and may contribute to its predicted docking profile. The involvement of



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further

Figure 3.2: Poseview 2D molecular interaction diagram of IMPHY003007 (Dihydrodehydrodiconiferyl alcohol) and MCL-1 protein

3. IMPHY012983 ((7R)-7-Hydroxylariciresinol)–MCL-1 Complex (Figure 3) IMPHY012983 ((7R)-7-Hydroxylariciresinol), the PoseView analysis demonstrated an extensive network of predicted hydrogen-bond interactions involving Gln211, His224, and Asn260, together with hydrophobic contacts involving Val216, Leu235, and Phe270. Aromatic interactions involving the ligand phenyl ring and Phe228 and Phe270 were also predicted. The combination of these interactions suggests favorable ligand–site complementarity within the MCL-1 binding region and may contribute to the compound's predicted docking profile. These structural features support the prioritization of IMPHY012983 as a promising computational candidate for further investigation. However, the predicted interactions do not establish binding affinity, selectivity, or inhibition of the anti-apoptotic activity of MCL-1, and these properties require experimental validation.

Figure 3.3:
Poseview 2D molecular interaction diagram of IMPHY012983 ((7R)-7-Hydroxylariciresinol) and MCL-1 protein

From a therapeutic perspective, the present computational findings provide a preliminary basis for further investigation of MCL-1 as a potential target in breast cancer. Previous studies have reported that MCL-1 inhibition may contribute to restoring apoptotic signaling and may have therapeutic relevance in different cancer contexts, including solid tumors. In this context, the identification of natural lignans and phenolic derivatives with favorable predicted interactions within the MCL-1 binding pocket provides a useful starting point for subsequent experimental investigation and lead optimization (Dong and Alahari, 2024; Bolomsky et al., 2020). However, the present docking results do not establish therapeutic efficacy or confirm MCL-1 inhibition, and these effects require experimental validation.

However, several limitations of this computational-only study must be acknowledged. First, molecular docking alone provides a static approximation of ligand binding, lacking dynamic temporal insight. Binding affinity does not necessarily translate to binding stability over time. Future studies should incorporate molecular dynamics (MD) simulations and free energy calculations (MM-PBSA/MM-GBSA) to refine binding predictions. Second, the use of in silico ADME analysis, while efficient, is inferential and should be validated experimentally using in vitro metabolic stability assessments. Finally, the biological relevance of these phytochemicals must be tested using cellular apoptosis assays, MCL-1 expression analysis, and competitive binding assays to confirm that observed interactions translate to functional inhibition of MCL-1 in breast cancer systems.

Conclusion

The findings provide preliminary computational evidence for the potential of Pinaceae-derived phytochemicals as MCL-1 inhibitory candidates. Among the screened compounds, IMPHY000001, IMPHY003007, and IMPHY012983 emerged as promising candidates based on their favorable docking scores, binding orientations, and interactions with residues within the MCL-1 binding site, together with acceptable drug-likeness characteristics. These findings suggest that the three compounds may have potential as starting points for further MCL-1 inhibitor development. However, the docking results should be considered predictive rather than definitive evidence of binding affinity or biological activity. Experimental validation, including biochemical binding and cellular assays, is required to confirm their ability to bind to and modulate MCL-1.

Recommendation

Based on the current findings, it is recommended that *invitro* and *in vivo* studies should be conducted to validate the recommended compounds by the *in silico* study.

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