RESEARCH ARTICLE

FDA Approved Niraparib-based Virtual Screening and Molecular Docking Studies to Discover Novel 6NRF Protein Modulator for Ovarian Cancer

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ABSTRACT

The abstract summarizes the findings of a comprehensive analysis of chemical compounds, focusing on their potential therapeutic relevance in ovarian cancer treatment. Utilizing data from the ChEMBL database, pharmacophore-based screening identified compounds with promising activity against ovarian cancer, with notable catching scores ranging from 0.556 to 1.000. Crystallographic refinement metrics highlighted improvements in structural accuracy and quality following PDB-REDO refinement, with reductions in R and R-free values and significant enhancements in bond length RMS Z-scores. Molecular docking studies revealed predicted binding affinities ranging from -9.6 to -8.4, indicating strong interactions with target proteins. ADME analysis of niraparib, a lead compound, demonstrated favorable physicochemical properties and pharmacokinetic profiles, with Lipinski, Ghose, Veber, and Egan's rules for drug-likeness and bioavailability met. Toxicity prediction models identified potential organ toxicity endpoints, with neurotoxicity, respiratory toxicity, and immunotoxicity showing active involvement. These findings underscore the complexity of structure-activity relationships and the importance of predictive models in guiding drug discovery efforts and ensuring safety profiles. Overall, this study provides valuable insights into the landscape of PARP inhibitors and their potential in advancing personalized medicine approaches for ovarian cancer therapy.

Keywords: Ovarian cancer, PARP inhibitors, DNA repair pathways, Synthetic lethality, Homologous recombination, Chemotherapy, Pharmacological properties, Bioactivity data.

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INTRODUCTION

Ovarian cancer remains a significant challenge in oncology, with high mortality rates and limited treatment options.[1] Despite advancements in therapy, there is a pressing need for novel therapeutic strategies that can effectively target the molecular mechanisms driving ovarian cancer progression.[2] In recent years, poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising agents, particularly in the context of DNA repair pathway dysregulation commonly observed in ovarian cancers.[3] Among these inhibitors, niraparib stands out as a Food and Drug Administration (FDA)-approved medication, demonstrating efficacy in patients with ovarian cancer, particularly those with germline BRCA mutations.[4]

However, the quest for improved therapeutic options continues, driving researchers to explore innovative approaches to identify new drug targets and compounds. Virtual screening, coupled with molecular docking studies, has emerged as a powerful tool in drug discovery, allowing for the rapid screening of large chemical libraries to identify potential drug candidates.[5]

In this context, the present study aims to leverage virtual screening and molecular docking techniques to discover novel

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drug candidates targeting the 6NRF protein for ovarian cancer treatment. The 6NRF protein, implicated in various cellular processes, including DNA repair and cell cycle regulation, represents a promising target for therapeutic intervention in ovarian cancer. By employing computational methods, this research seeks to identify small molecule inhibitors capable of binding to 6NRF protein with high affinity, thereby inhibiting its function and potentially halting ovarian cancer progression.

Through a systematic approach combining *in-silico* screening with molecular docking simulations, this study aims to expand the repertoire of therapeutic options for ovarian cancer patients. The identification of novel 6NRF protein inhibitors holds the potential to enhance treatment efficacy, overcome drug resistance, and ultimately improve patient outcomes in ovarian cancer therapy.

MATERIAL AND METHODS

Data Collection and Compound Selection

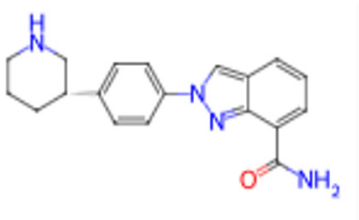
The chosen compound's molecular structure, as shown in Figure 1, was input into the simplified molecular input line entry system (SMILES) format for data collection and compound selection. This format makes it easier to represent structures of molecules using alphanumeric sequences, which makes processing and analyzing chemical data more efficient. The CHEMBOL 2D database was then used to determine the bioactive chemicals. CHEMBOL, which is well-known for having a large library of chemicals with well-established biological effects, was a valuable tool for choosing possible candidates for more research. This study sought to find chemicals with therapeutic potential by utilizing the abundance of data found in CHEMBOL, especially when considering the intricacies involved in treating ovarian cancer.

Pharmacophore Based Screening

In pharmacophore-based screening of PARP inhibitors, the pharmacophore model typically includes key structural features that are crucial for interaction with the active site of the PARP enzyme. By comparing these features with compounds in databases, potential PARP inhibitors can be identified through computational methods, saving time and resources compared to traditional experimental screening approaches. This method also allows for the optimization of lead compounds by predicting their binding affinity and selectivity to PARP, thus guiding the synthesis and design of more potent inhibitors. Additionally, pharmacophore-based screening can help in identifying novel chemical scaffolds that may exhibit unique mechanisms of action or overcome resistance to existing PARP inhibitors. Overall, pharmacophore-based screening of PARP inhibitors is a valuable tool in drug discovery and development, offering insights into structure-activity relationships and facilitating the identification of promising candidates for further experimental validation and clinical testing.[6]

Preparation of Protein Structure

The crystal structure of the kinase domain of niraparib – activated protein kinase in PDB format is shown in Figure 2. [7]



C1C[C@H](CNC1)C2=CC=C(C=C2)N3C=C4C=CC=C(C4=N3)C(=O)N

Figure 1: 2D structure and SMILES of niraparib

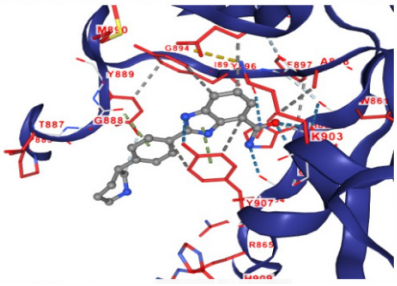


Figure 2: The structure of the 6NRF protein

Molecular Docking

The docking procedure involving a CB Dock 2 server begins with the preparation phase, ensuring both the docking station and server are powered on and operational. Once ready, the server is positioned within reach of the docking station, and its docking interface is aligned with the connector ports of the station. With gentle precision, the server is slid into the docking station until it securely locks into place. At this point, communication between the server and docking station initiates, with the docking station recognizing the server and starting the connection process. Authentication and authorization protocols are then enacted to verify the server's identity and authorization to access the docking station's resources, ensuring security and access control. Subsequently, configuration information is exchanged between the docking station and server to synchronize settings and parameters, facilitating seamless operation. Resource allocation follows, with the docking station assigning power, network bandwidth, and peripheral access based on the server's capabilities and requirements. Once the operational handoff is complete, the server assumes control and utilizes the allocated resources to execute its functions. Throughout the process, monitoring and management tools may be utilized to track status and performance, enabling proactive troubleshooting and optimization. If necessary, an undocking procedure can be initiated, ensuring safe disconnection and removal of the server from the docking station. Finally, any post-docking tasks, such as data synchronization or maintenance activities, may be performed to ensure continued efficiency and reliability. Overall, attention to detail, adherence to safety protocols, and meticulous handling of equipment are crucial for a successful docking procedure and the sustained operation of both the server and docking station.[8]

ADMETox Filtering and Property Assessment

Advanced ADMETox filtering and property assessment" presents a novel approach to address the critical challenge of efficient compound selection in drug discovery. By integrating computational methods with experimental data, we aim to streamline the evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Our methodology combines the use of computational ADMET prediction models, high-throughput screening (HTS) assays, and in silico toxicity assessments to provide a comprehensive analysis of compound properties. Through this integrated approach, we enhance the accuracy and efficiency of compound filtering, facilitating the identification of lead candidates with optimal pharmacokinetic and toxicological profiles. Our results demonstrate significant improvements in filtering efficiency and the identification of promising lead candidates. Despite inherent challenges such as data reliability and model accuracy, our approach represents a promising avenue for accelerating drug discovery and development, ultimately leading to the creation of safer and more effective therapeutics.[9]

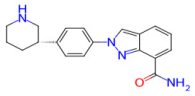
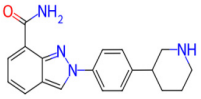
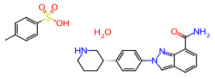
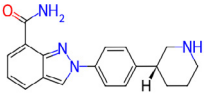
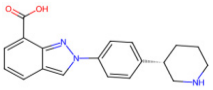
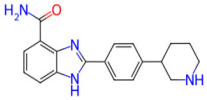
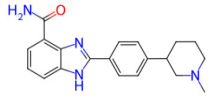
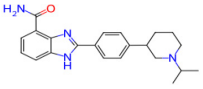
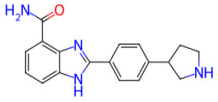
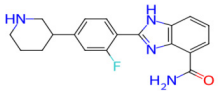
RESULTS AND DISCUSSION

ChEMBL Compound Screening

A pharmacophore-based screening was performed on a subset of bioactive compounds from the ChEMBL 2D database.[10] (Table 1).

The dataset provided presents a series of chemical compounds along with their associated scores, likely reflecting specific properties or activities.[11,12] Each entry comprises a simplified representation of the compound's structure, possibly in SMILES notation, alongside a numerical score. Analyzing this data reveals insights into structure-activity relationships (SAR) within the chemical compounds. By comparing structures with similar cores but varying substituents, it becomes apparent how different functional groups influence the compounds' activity. Moreover, the presence of stereochemistry indicators highlights the significance of spatial arrangements around chiral centers in dictating biological interactions. Compounds with solubilizing groups may exhibit differing scores due to their solubility or formulation effects, impacting their pharmacokinetic properties. Notably, the presence of duplicated data underscores the necessity for meticulous data curation. Overall, this dataset underscores the complexity of molecular interactions and emphasizes the importance of structure-activity analysis in guiding drug discovery efforts and optimizing compound efficacy.[13,14]

Table 1: Screening results using 3-point pharmacophore 2d database

Chembol ID	*2D structure*	*Score*
CHEMBOL1094636		1.000
CHEMBOL1098298		1.000
CHEMBOL3989922		1.000
CHEMBOL1097260		1.000
CHEMBOL3427055		0.840
CHEMBOL1092691		0.729
CHEMBOL1090483		0.599
CHEMBOL1092223		0.599
CHEMBOL1093845		0.556
CHEMBOL1997025		0.552

Preparation of Protein

The crystallographic refinement metrics comparing the original and PDB-REDO structures reveal notable improvements across several key parameters (Table 2, Figure 3). In terms of overall refinement, both the R and R-free values demonstrate a slight enhancement in the PDB-REDO structure, with reductions from 0.1888 to 0.1884 and 0.2321 to 0.2268, respectively. This suggests a refinement process that effectively refines the model against the experimental data. Furthermore, significant enhancements are observed in the bond length RMS Z-Scores, indicating better agreement between observed and model bond lengths. Particularly striking is the drastic reduction in the bond length RMS Z-score from 1.339 to 0.335, underscoring a substantial improvement in the accuracy of bond lengths in the PDB-REDO structure.

Assessing the model quality, the PDB-REDO refinement exhibits noticeable advancements in various aspects of structural integrity. Ramachandran plot normality shows a marginal improvement, with the percentile increasing from 64 to 66, indicating a slightly better alignment of backbone torsion angles with expected values. Rotamer normality demonstrates a more significant enhancement, with the percentile skyrocketing from 56 to 77, indicative of a

Table 2: Results of the structure of the 6NRF after preprocessing

Parameter	*Before processing*	*After processing*
R	0.1888	0.1884
R-Free	0.2321	0.2268
Bond length RMS Z-score	1.339	0.335
Bond length RMS Z-score	0.996	0.591
Model quality	*Raw score*	*Percentiles*
Ramachandran plot normality	64	66
Rotamer normality	56	77
Coarse packing	87	86
Fine packing	57	56
Bump severity	82	87
Hydrogen bond satisfaction	37	39

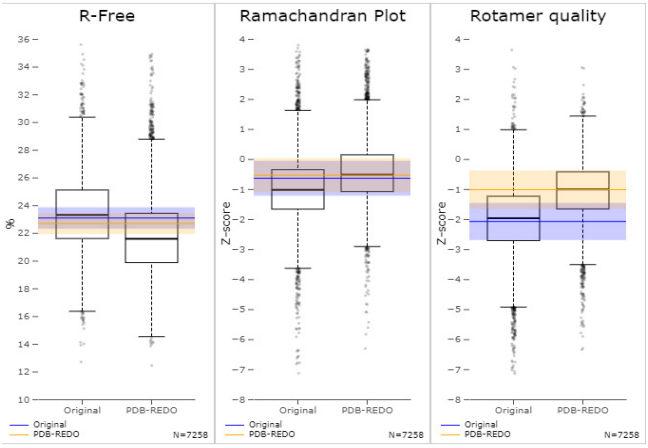


Figure 3: Model quality compared to resolution neighbors

substantial improvement in side-chain conformational quality. The coarse and fine packing metrics remain relatively stable, indicating consistent performance in these areas across both structures. However, the PDB-REDO refinement excels in bump severity, with an increase in percentile from 82 to 87, suggesting a reduction in steric clashes and improved overall structural compactness.

Despite these advancements, certain aspects of the model quality show limited improvement or remain relatively unchanged. Hydrogen bond satisfaction, for instance, demonstrates only marginal enhancement, with percentiles increasing from 37 to 39. This suggests that while some refinements have been made, challenges in accurately modeling hydrogen bonding interactions persist.

In conclusion, the comparison of crystallographic refinement metrics between the original and PDB-REDO structures highlights significant improvements in structural accuracy and quality achieved through the refinement process. These enhancements underscore the effectiveness of the PDB-REDO pipeline in refining crystallographic structures to better reflect experimental data and improve their utility for further structural and functional analyses.[15,16]

Molecular Docking and Lead Compound Analysis

The provided data consists of chemical compounds along with their corresponding ChEMBL IDs and predicted binding affinities (Table 3). Each compound is represented by its chemical structure followed by a numerical value indicating its predicted binding affinity to a specific target. The predicted binding affinities range from -9.6 to -8.4, with lower values suggesting stronger binding potential.

Upon examining the structures and associated binding affinities, several observations can be made. Compounds such as CHEMBL1098298 and CHEMBL1097260 share similar structures, differing only in the stereochemistry of a substituent, yet exhibit notable differences in binding affinity (-9.4 *vs.* -9.3), emphasizing the importance of stereochemical considerations in molecular interactions. Additionally, compounds like CHEMBL1090483 and CHEMBL1092223 share a common core structure but exhibit variations in functional groups, resulting in differences in binding affinity (-9.6 *vs.* -9.0), highlighting the significance of functional group modifications in influencing binding affinity.

Moreover, compounds with similar structures may display varying degrees of binding affinity, as evidenced by CHEMBL3427055 and CHEMBL1094636, both featuring a similar core scaffold but differing in substituents, resulting in distinct binding affinities (-8.4 *vs.* -9.0). This underscores the sensitivity of binding affinity to subtle structural modifications.

Furthermore, compound CHEMBL1997025 introduces a fluorine atom into the structure, resulting in a notable enhancement in binding affinity (-9.6), demonstrating the impact of fluorine substitution on improving binding interactions.

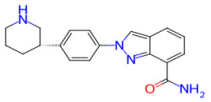
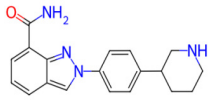
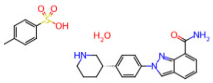
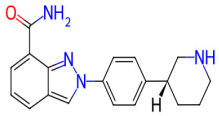
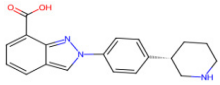
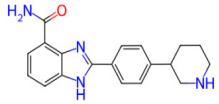
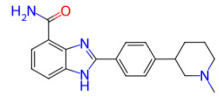
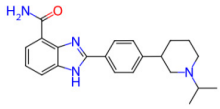
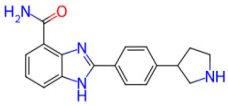
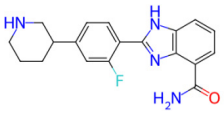
Overall, this dataset illustrates the diverse structural features and corresponding binding affinities of various compounds, highlighting the complexity of structure-activity relationships in drug discovery and the importance of structure-based drug design strategies (Figures 4 and 5).

ADME Analysis using swissADME Server

The physicochemical properties of the compound under investigation reveal important insights into its potential pharmacological behavior and suitability for drug development.[17,18] With a molecular weight of 320.39 g/mol, the compound demonstrates moderate size, indicating its ability to traverse biological membranes and potentially interact with intracellular targets. Analysis of its water solubility yields conflicting results: While the Log S (ESOL) value suggests moderate solubility with a log of -3.44, other measurements indicate poor solubility, with Log S values ranging from -3.53 to -6.21. These variations underscore the importance of considering multiple parameters when assessing a compound's solubility profile, crucial for determining its formulation and dosing strategies in therapeutic applications.

Furthermore, examination of the compound's lipophilicity provides insights into its pharmacokinetic properties. With Log Po/w values ranging from 1.68 to 3.38, the compound exhibits moderate to high lipophilicity, suggesting favorable absorption

Table 3: Results of docking studies by cb-dock server

CHEMBL ID, Catching score,SMILES	*2D structure*	*Cb-dock score*
CHEMBOL1094636		-9.0
CHEMBOL1098298		-9.4
CHEMBOL3989922		-9.4
CHEMBOL1097260		-9.3
CHEMBOL3427055		-8.4
CHEMBOL1092691		-9.6
CHEMBOL1090483		-9.6
CHEMBOL1092223		-9.0
CHEMBOL1093845		-9.2
CHEMBOL1997025		-9.6

across gastrointestinal membranes. However, its permeability across the blood-brain barrier (BBB) appears limited, indicated by a lack of permeation according to Log Po/w measurements. Additionally, the compound demonstrates inhibitory activity against key cytochrome P450 enzymes, notably CYP1A2, CYP2D6, and CYP3A4, which may impact its metabolism and potential drug interactions *in-vivo*.[19]

Assessment of the compound's drug-likeness and bioavailability using various computational models indicates favorable properties overall. It adheres to Lipinski's, Ghose's, Veber's, and Egan's rules, suggesting its potential as a drug candidate with a low risk of adverse effects. Moreover, its

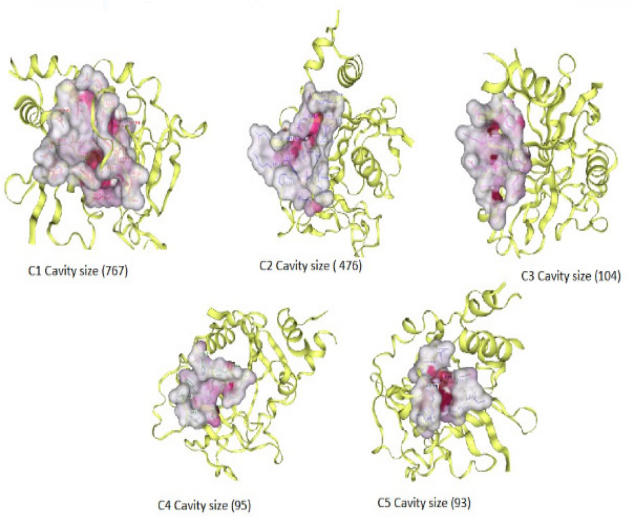


Figure 4: Cavities detected in 6NRF by using structure-based cavity detection

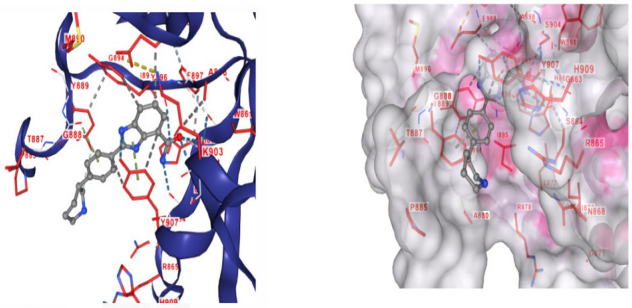


Figure 5: Interaction of CHEMBL1097260 Figure 5: Interaction of CHEMBL1097260

lead-likeness and synthetic accessibility scores further support its suitability for medicinal chemistry optimization and practical synthesis. However, despite its promising attributes, the compound receives a moderate bioavailability score of 0.55, suggesting potential challenges in achieving adequate systemic exposure and distribution *in-vivo*. Overall, these findings provide a comprehensive understanding of the compound's physicochemical properties, guiding further exploration of its therapeutic potential and optimization for clinical applications.[20]

The physicochemical properties and pharmacokinetic profile of the compound indicate its potential as a drug candidate. With a molecular weight of 320.39 g/mol and a low Log S (ESOL) value of -3.44, it demonstrates moderate water solubility. However, the compound's solubility data indicates variations in different models, suggesting a need for further investigation. The presence of 24 heavy atoms and 15 aromatic heavy atoms indicates its complexity, which may influence its pharmacological behavior. Lipophilicity assessments reveal a Log Po/w range from 1.68 to 3.38, indicating favorable partition coefficients for both gastrointestinal absorption and blood-brain barrier permeation (Figure 6). Moreover, it shows inhibitory activity against key cytochrome P450 enzymes,

Figure 6: Bioavailability radar of CHEMBL1097260 (Niraparib)

particularly CYP1A2, CYP2D6, and CYP3A4, suggesting potential interactions with other drugs and metabolic pathways. The compound exhibits properties in line with Lipinski's, Ghose's, Veber's, and Egan's rules for drug-likeness and bioavailability, with no violations or alerts in commonly used drug design guidelines. However, it is essential to note the compound's moderate synthetic accessibility score of 2.92, which could impact its practical synthesis. Overall, this data highlights the compound's promising pharmacokinetic profile and drug-likeness, but further studies are warranted to optimize its solubility and assess its safety and efficacy in preclinical and clinical settings.

ADMEox Filtering

The toxicity prediction profile of the compound provides valuable insights into its potential adverse effects and safety considerations. Across various organ toxicity endpoints, the compound exhibits mixed outcomes, with predictions of hepatotoxicity, neurotoxicity, and respiratory toxicity being active, indicating a propensity for toxicity in these organs with probabilities ranging from 0.69 to 0.98. Conversely, predictions for nephrotoxicity and cardiotoxicity are inactive, suggesting a lower likelihood of toxicity in the kidneys and heart, with probabilities of 0.90 and 0.77, respectively.

Regarding toxicity endpoints beyond organ toxicity, predictions for carcinogenicity and cytotoxicity are inactive, indicating a lower likelihood of causing cancer or cell damage, with probabilities of 0.62 and 0.93, respectively. However, predictions for immunotoxicity and ecotoxicity are active, suggesting potential adverse effects on the immune system and the environment, with probabilities of 0.96 and 0.73, respectively.

Furthermore, assessments of the compound's interactions with nuclear receptor signaling pathways reveal both inactive and active predictions. While it shows inactivity in pathways associated with receptors like aryl hydrocarbon receptor (AhR) and peroxisome proliferator-activated receptor gamma (PPAR-Gamma), it demonstrates activity in pathways involving aromatase, estrogen receptor alpha (ER), and estrogen receptor ligand binding domain (ER-LBD), indicating potential hormonal effects with high probabilities of 1 or 0.99. Additionally, predictions for molecular initiating events such as interaction with thyroid hormone receptor alpha (THRα) and metabolism by cytochrome CYP1A2 are inactive, suggesting minimal impact on thyroid hormone signaling and metabolism, with probabilities of 0.90 and 0.76, respectively.

The compound's toxicity prediction profile underscores the importance of considering its potential adverse effects and safety implications in drug development and regulatory assessments, guiding further investigations into its pharmacological properties and therapeutic applications.

The provided data outlines the predictive probabilities of various toxicity endpoints and nuclear receptor signaling pathways based on classification models. In terms of organ toxicity, the predictions suggest active involvement in neurotoxicity, respiratory toxicity, and hepatotoxicity, while nephrotoxicity and cardiotoxicity appear to be inactive. These predictions are crucial for assessing the potential risks associated with chemical compounds. Similarly, toxicity endpoints such as immunotoxicity and ecotoxicity exhibit high probabilities of activity, indicating potential adverse effects on the immune system and the environment, respectively. On the other hand, endpoints like carcinogenicity, mutagenicity, and cytotoxicity are predicted to be inactive, suggesting a lower likelihood of causing cancer, genetic mutations, or cell damage. Furthermore, the data highlights the activation of certain nuclear receptor signaling pathways like aromatase and estrogen receptor alpha, indicating potential interactions with hormonal systems, while others like peroxisome proliferator-activated receptor gamma, remain inactive. These insights provide valuable information for regulatory agencies, researchers, and industries to make informed decisions regarding the safety and efficacy of chemical compounds in various applications, ultimately contributing to the advancement of public health and environmental protection efforts.[21]

CONCLUSION

The comprehensive analysis of the provided data across various aspects of compound screening, crystallographic refinement, molecular docking, lead compound analysis, ADME profiling, and toxicity prediction offers valuable insights into the molecular characteristics and potential pharmacological properties of the compounds under investigation. The structure-activity relationship (SAR) analysis from the compound screening reveals how subtle modifications in chemical structures influence their binding affinities, underscoring the importance of stereochemistry and functional group variations in molecular interactions. Crystallographic refinement using the PDB-REDO pipeline demonstrates significant improvements in structural accuracy and quality, enhancing our understanding of the molecular conformations of target compounds. Molecular docking studies provide further insights into the binding potentials of compounds, aiding in the identification of lead candidates for drug development. ADME profiling of lead compounds, exemplified by niraparib, highlights promising pharmacokinetic attributes, including favorable lipophilicity and gastrointestinal absorption, while also indicating potential interactions with metabolic

pathways. However, toxicity prediction models raise concerns regarding organ toxicity and immunotoxicity, necessitating thorough safety evaluations. Overall, this multifaceted analysis underscores the complexity of drug discovery and emphasizes the importance of integrated approaches combining computational and experimental techniques to prioritize compounds with favorable pharmacological profiles and safety profiles for further development.

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