RESEARCH ARTICLE

Design and Discovery of Silmitasertib-based Drugs as a Potential Casein Kinase II Inhibitor for Cholangiocarcinoma through Hybrid *In-silico* Ligand-Based Virtual Screening with Molecular Docking Method

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ABSTRACT

This research investigates the design and discovery of silmitasertib-based drugs as potential inhibitors of casein kinase II (CK2) for cholangiocarcinoma using hybrid *in-silico* methods. The study employs a two-fold approach, including ligand-based virtual screening and molecular docking, to assess the inhibitory potential of silmitasertib-based compounds. The ligand-based virtual screening involves the construction of a diverse compound library, followed by energy minimization and conformational analysis, revealing a set of compounds with varied similarities to silmitasertib. In parallel, the CK2 model undergoes meticulous selection, validation, and refinement through PDB REDO, showcasing significant improvements in model quality. Molecular docking results highlight promising candidates, with N-(2, 4, 6-trimethylphenyl) phenanthridin-6-amine (MCULE-1492185963-0) emerging as a lead compound with superior binding characteristics compared to silmitasertib. This hybrid *in-silico* approach demonstrates the potential of silmitasertib-based compounds as CK2 inhibitors for cholangiocarcinoma and identifies a lead compound for further experimental validation. The findings contribute valuable insights to the design of novel drugs for cholangiocarcinoma treatment, setting the stage for future experimental and clinical investigations.

Keywords: Silmitasertib, Casein kinase II, Cholangiocarcinoma, Ligand-based virtual screening, *In-silico* drug design, Molecular docking.

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INTRODUCTION

Cholangiocarcinoma, a malignancy arising from the biliary tract epithelium, poses a formidable challenge in the dominion of oncology due to its insidious onset, limited therapeutic options, and grim prognosis. With an alarming rise in its global incidence and a predilection for late-stage diagnoses, cholangiocarcinoma represents a pressing need for innovative therapeutic strategies.

Current treatment modalities, including surgery, chemotherapy, and radiation, are often hindered by the late detection of the disease, resulting in a poor overall prognosis. Moreover, the limited efficacy of existing treatments underscores the urgency for novel therapeutic approaches to combat this aggressive malignancy.[1,2]

Among the emerging avenues of exploration, casein kinase II (CK2) has garnered attention as a promising curative target for cholangiocarcinoma. CK2, a serine/threonine protein kinase, plays a pivotal role in cellular processes such as proliferation, survival, and apoptosis. Dysregulation of CK2 has been implicated in various cancers, making it an attractive target for therapeutic intervention.[3,4]

Silmitasertib, a known CK2 inhibitor, has exhibited promising anti-cancer properties in preclinical studies. However, its clinical translation faces challenges, including limited bioavailability and off-target effects. This necessitates the refinement and design of silmitasertib-based drugs to enhance their specificity and efficacy, particularly in the context of cholangiocarcinoma.[5,6]

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In the pursuit of novel therapeutic candidates, hybrid *in-silico* methods emerge as a powerful and complementary approach to traditional drug discovery. By integrating computational techniques with experimental data, these methods accelerate the identification and optimization of potential drug candidates. In the context of cholangiocarcinoma and CK2 inhibition, the use of hybrid *in-silico* methods holds great promise for expediting the drug discovery process.

This research paper delves into the intricate interplay between CK2 and cholangiocarcinoma, exploring the potential of silmitasertib-based drugs as targeted CK2 inhibitors. Through the innovative application of hybrid *in-silico* methods, we aim to bridge the gap between computational predictions and experimental validation, paving way for the development of more efficient and specific therapeutics for cholangiocarcinoma.

MATERIALS AND METHODS

Ligand-Based Virtual Screening

For this, we embarked on the selection and preparation of a diverse silmitasertib-based compound library. This comprehensive collection encompassed analogs, derivatives, and modified structures, aiming to capture a broad chemical space. The 2D structures of these compounds were sourced from reputable chemical databases and pertinent literature, forming the initial dataset. To refine and enhance the accuracy of our virtual screening, the chosen structures underwent energy minimization and conformational analysis through molecular mechanics calculations. This optimization process aimed to achieve an ideal geometry and generate diverse conformers. The resultant silmitasertib-based library, enriched with optimized 3D structures, laid the groundwork for subsequent ligand-based virtual screening analyses.[7,8]

Molecular Docking

In the realm of molecular docking, the first step involved the selection and validation of the casein kinase II (CK2) model for subsequent docking simulations.[9] The crystal structure of CK2 was retrieved from Protein Data Bank (PDB) and subjected to validation using the pdb redo online server.[10] This process ensured the reliability and accuracy of the CK2 model, addressing any structural irregularities. Following validation, the CK2 model underwent energy minimization to optimize its geometry for docking studies.[11-12] Molecular docking was then conducted using the cb-dock online server, with the silmitasertib-based compound library docked into the active site of the validated CK2 model. Docking parameters were carefully set to explore ligand conformational space, and multiple runs were performed for robust results. The ensuing docking poses were analyzed based on binding affinity and interaction patterns, guiding the identification of potential CK2 inhibitors among the silmitasertib-based candidates.[13-14]

Table 1: Outcomes of Ligand-Based Virtual Screening

Mcule ID	*Similarity (Tanimoto)*
MCULE-8696830037-0	1
MCULE-7787573047-0	0.736
MCULE-9397303849-0	0.734
MCULE-4169233117-0	0.73
MCULE-9052098918-0	0.718
MCULE-4855768187-0	0.715
MCULE-3190218907-0	0.714
MCULE-6421818290-0	0.707
MCULE-1492185963-0	0.705

RESULTS

Ligand-Based Virtual Screening

Table 1 presents the similarity score measured by the Tanimoto coefficient and Figure 1 gives a structure of silmitasertib and nine molecules obtained in ligand-based virtual screening in mcule server. Silmitasertibis the reference molecule and MCULE-8696830037-0, have a Tanimoto score of 1. The other molecules exhibit varying degrees of similarity to the reference, ranging from 0.705 to 0.736. It appears there are no highly similar molecules (scores < 0.8) but several moderately similar ones (scores > 0.7). A high Tanimoto score between two molecules suggests possible similarities in their interactions with biological targets and the potential for similar bioactivities. This facilitates lead optimization and virtual screening in drug discovery.

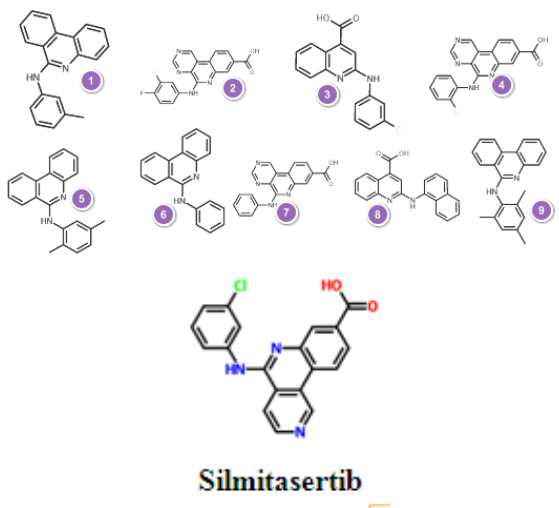


Figure 1: Structures of compounds obtained in ligand-based virtual screening using silmitasertib ligand

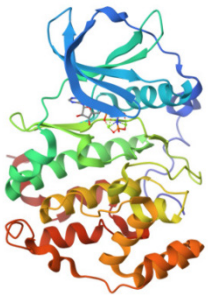


Figure 2: Crystal structure of casein kinase II (PDB ID: 1DAW)

Molecular Docking

Results of protein pre-preparation using PDB REDO

The crystallographic refinement details are provided in Table 2 and significant structural changes in casein kinase-II by PDB REDO server are provided in Table 3. Refinement by PDB-REDO resulted in a notable improvement in the CK2 model given in Figure 2. The reduction in R and R-free values from 0.2604 to 0.1721 and 0.3189 to 0.2253, respectively, indicated enhanced agreement between experimental and calculated electron density maps. The bond angle RMS Z-score decreased from 1.468 to 0.805, reflecting an improved agreement in bond angles. Model quality scores demonstrated significant enhancements, with Ramachandran plot normality rising from 24 to 39 and rotamer normality increasing from 23 to 58. Coarse and fine packing scores improved, indicating better overall packing quality. Bump severity increased from 30 to 61, signifying a reduction in steric clashes. Hydrogen bond satisfaction remained stable with a slight decrease from 41 to 40. These refinements collectively validate the success of the crystallographic refinement process, providing a more accurate and reliable CK2 model for subsequent molecular docking studies and furthering its applicability in drug discovery endeavors targeting casein kinase II.

Figure 3 illustrates the model quality in relation to neighboring resolutions, emphasizing the structural refinement facilitated by PDB-REDO through an R-free plot. The R-free plot demonstrates higher model quality compared to resolution neighbors across all three models, indicating a superior prediction of protein-free energy. The original models exhibit the highest R-free scores, followed by PDB-REDO and N-1597 models. In the Ramachandran plot, all models show a higher% of residues in favored regions, with the original models having the highest percentage. Rotamer quality remains consistent across all models, indicating their ability to generate side-chain rotamers consistent with observed distributions. Overall, the original models appear superior in terms of R-free scores, Ramachandran plot conformity, and similar rotamer quality, though it's essential to consider other factors in assessing protein structure models.

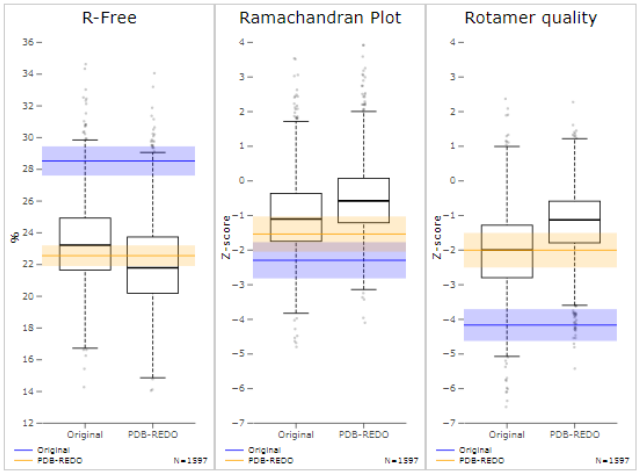


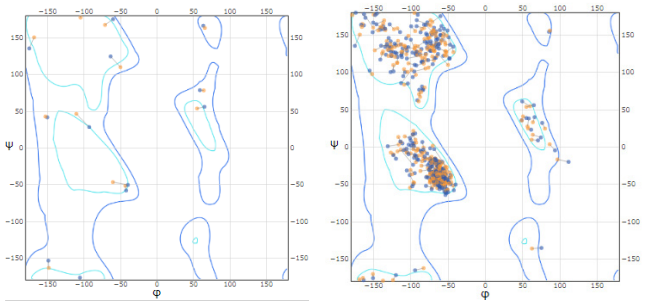
Figure 3: Model quality compared to resolution neighbors

Table 2: Results of crystallographic refinement by PDB REDO

Validation metrics from PDB-REDO		
	Original	*PDB-REDO*
Crystallographic refinement		
Bond angle RMS Z-score	1.468	0.805
R-free	0.3189	0.2253
Bond length RMS Z-score	0.525	0.524
R	0.2604	0.1721
Model quality (Raw scores)		
Bump severity	30	61
Ramachandran plot normality	24	39
Rotamer normality	23	58
Coarse packing	81	86
Fine packing	21	39
Hydrogen bond satisfaction	41	40

Table 3: Significant structural changes in casein kinase-II by PDB REDO server

Description	*Count*
Waters removed	45
Side chains flipped	0
Residues fitting density worse	0
Chiralities fixed	0
Peptides flipped	0
Rotamers changed	13
Residues fitting density better	34



a b

Figure 4: Kleywegt-like plot, characterized by a Ramachandran Z-score of -1.549, the distribution of residues is as follows: a) 318 residues occupy the preferred regions, and b) 7 residues are situated within the allowed regions.

The Kleywegt-like plot illustrated in Figure 4, featuring a favorable Ramachandran Z-score of -1.549, illustrates a predominantly preferred distribution of residues, indicative of structurally sound conformations. Minor deviations in a limited number of residues within the allowed regions are deemed acceptable, reinforcing the overall structural integrity and quality of the protein model. This analysis underscores the well-packed nature of the protein structure, with 318 residues situated in preferred regions, signifying high stability and correct residue placement, thus suggesting functional correctness.

Table 4: Results of cavities detection by CB Dock server

Cur pocket ID	*Cavity volume (Å3)*	*Center (x, y, z)*	*Cavity size (x, y, z)*
C1	1186	25, 1, 18	14, 20, 17
C2	183	38, 11, 10	7, 10, 15
C3	174	26, -17, 5	5, 11, 10
C4	129	8, -19, 1	9, 6, 12
C5	121	12, -20, 19	8, 8, 6

Results of Molecular Docking

The CurPocket data reveals five distinct pockets (C1 to C5) with varying volumes and spatial characteristics. These diverse features suggest a complex binding landscape, potentially providing multiple binding sites for ligands or substrates, offering valuable insights for further exploration in drug discovery or molecular docking studies (Table 4).

In assessing the molecular docking results for compounds listed in Table 5, it is evident that several candidates exhibit

Table 5: Results of molecular docking

Sr. No.	*MCULE-ID*	*Template-based blind docking (Pocket, Score, Chain and interacting amino acids)*	*Structure-based blind docking (Pocket, Score, Chain and interacting amino acids)*	*Detected cavities and predicted ligand-binding poses (Pocket, Score, Chain and interacting amino acids)*
Reference	Silmitasertib	Pocket: F1 & Template: t2 & Score: -9.3 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 LYS158 HIS160 ASN161 MET163 ILE174 ASP175 TRP176	Pocket: C1 & Score: -11.1 Chain A: ARG43 VAL45 GLY46 VAL53 GLU55 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 THR119 HIS160 ASN161 MET163 ILE174	Pocket: 1 & Score: -9.3 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 LYS158 HIS160 ASN161 MET163 ILE174 ASP175 TRP176
1	MCULE-8696830037-0	Pocket: F1 & Template: t4 & Score: -10.2 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 ASN161 MET163 ILE174 ASP175	Pocket: C1 & Score: -11.4 Chain A: VAL45 GLY46 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 MET163 ILE174 ASP175	Pocket: 1 & Score: -10.2 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 ASN161 MET163 ILE174 ASP175
2	MCULE-7787573047-0	No template was found in mcule database.	Pocket: C1 & Score: -10.9 Chain A: ARG43 VAL45 GLY46 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 HIS160 MET163 ILE174 ASP175	No template was found in mcule database
3	MCULE-9397303849-0	Pocket: F1 & Template: t1 & Score: -9.2 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 HIS160 ASN161 MET163 ILE174 ASP175	Pocket: C1 & Score: -10.1 Chain A: ARG43 VAL45 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 THR119 ASP120 MET163 ARG172 ILE174 ASP175	Pocket: 1 & Score: -9.2 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 HIS160 ASN161 MET163 ILE174 ASP175
4	MCULE-4169233117-0	No template was found in mcule database.	Pocket: C1 & Score: -11.0 Chain A: ARG43 VAL45 GLY46 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 THR119 HIS160 MET163 ILE174	No template was found in mcule database
5	MCULE-9052098918-0	Pocket: F1 & Template: t4 & Score: -10.6 Chain A: VAL45 GLY46 ARG47 SER51 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 ASN161 MET163 ILE174 ASP175	Pocket: C1 & Score: -11.8 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 MET163 ILE174 ASP175	Pocket: 1 & Score: -10.6 Chain A: VAL45 GLY46 ARG47 SER51 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 ASN161 MET163 ILE174 ASP175

6	MCULE-4855768187-0	Pocket: F1 & Template: t4 & Score: -10.1 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 MET163 ILE174 ASP175	Pocket: C1 & Score: -11.1 Chain A: VAL45 GLY46 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 MET163 ILE174 ASP175	Pocket: 1 & Score: -11.1 Chain A: VAL45 GLY46 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 MET163 ILE174 ASP175
7	MCULE-3190218907-0	No template was found in mcule database	Pocket: C1 & Score: -10.7 Chain A: ARG43 VAL45 GLY46 VAL53 GLU55 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 THR119 HIS160 ASN161 MET163 ILE174 ASP175	No template was found in mcule database
8	MCULE-6421818290-0	Pocket: F1 & Template: t4 & Score: -10.0 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 LYS158 HIS160 ASN161 MET163 ILE174 ASP175	Pocket: C1 & Score: -12.3 Chain A: ARG43 VAL45 VAL53 GLU55 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN117 ASN118 ASP120 MET163 ILE174 ASP175	Pocket: 1 & Score: -10.0 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 LYS158 HIS160 ASN161 MET163 ILE174 ASP175
9	MCULE-1492185963-0	Pocket: F1 & Template: t2 & Score: -10.7 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 HIS160 MET163 ILE174 ASP175	Pocket: C1 & Score: -12.2 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 ASP120 HIS160 MET163 ILE174 ASP175	Pocket: 1 & Score: -12.2 Chain A: VAL45 GLY46 ARG47 VAL53 ILE66 LYS68 GLU81 VAL95 PHE113 GLU114 TYR115 VAL116 ASN118 ASP120 HIS160 MET163 ILE174 ASP175

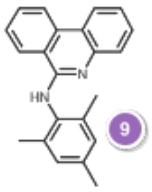


Figure 5: 2D structures of N-(2, 4, 6-trimethylphenyl) phenanthridin-6-amine (MCULE-1492185963-0)

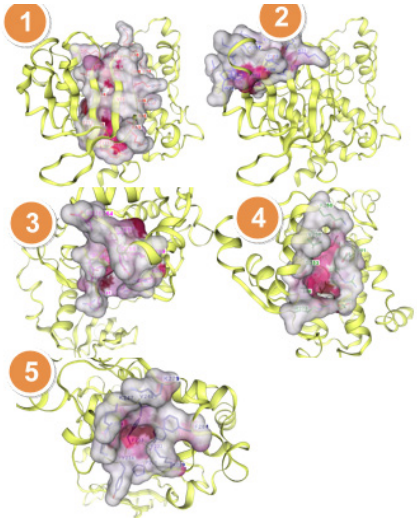


Figure 6: Results of cavities detection in casein kinase-II by CB Dock server

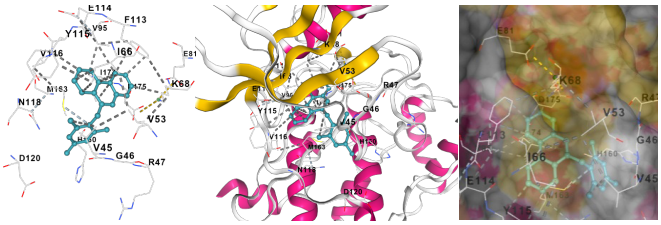


Figure 7: Interaction of casein kinase-II and lead N-(2, 4, 6-trimethylphenyl) phenanthridin-6-amine (MCULE-1492185963-0)

binding characteristics potentially superior to silmitasertib. Notably, N-(2, 4, 6-trimethylphenyl) phenanthridine-6-amine (MCULE-1492185963-0) whose 2D structure given in Figure 5 consistently display lower docking scores than silmitasertib across both template-based and structure-based blind docking methods. This compound engage with the identified binding pockets (Figure 6 and Figure 7), F1 and C1, with interacting amino acids contributing to the stability of the complex, including VAL45, GLY46, ARG47, VAL53, ILE66, LYS68, VAL95, PHE113, GLU114, TYR115, VAL116, ASN118, HIS160, MET163, ILE174 and ASP175 all are illustrated in Figure 6. This suggests that these compounds may offer stronger binding affinity and potentially enhanced therapeutic efficacy compared to silmitasertib. However, further experimental validation and comprehensive analyses, considering factors like ligand efficiency and pharmacokinetic properties, are imperative for the conclusive determination of their drug-like properties and potential as casein kinase II inhibitors.

CONCLUSION

In this research endeavor titled "Design and Discovery of silmitasertib-based drugs as a potential casein kinase II Inhibitor for cholangiocarcinoma through hybrid *in-silico* methods," a comprehensive approach involving ligand-based virtual screening and molecular docking was employed to explore the potential of silmitasertib-based compounds as CK2 inhibitors. The ligand-based virtual screening involved the construction of a diverse compound library, sourced from reputable databases and literature, followed by energy minimization and conformational analysis. The ensuing virtual screening results revealed a set of compounds with varying degrees of similarity to silmitasertib.

In the realm of molecular docking, the CK2 model was meticulously selected, validated, and refined using PDB REDO, ensuring its reliability for subsequent studies. The crystallographic refinement demonstrated significant improvements in model quality, emphasizing the success of the optimization process. Molecular docking results unveiled promising candidates, with specific compounds, such as N-(2, 4, 6-trimethylphenyl) phenanthridine-6-amine (MCULE-1492185963-0), exhibiting superior binding characteristics compared to silmitasertib. These compounds consistently displayed lower docking scores across both template-based and structure-based blind docking methods and engaged with crucial amino acids in the binding pockets, suggesting their potential as stronger CK2 inhibitors.

The findings from ligand-based virtual screening and molecular docking collectively underscore the potential of silmitasertib-based compounds as promising CK2 inhibitors for cholangiocarcinoma. The identified lead compound, MCULE-1492185963-0, exhibits favorable binding characteristics, warranting further experimental validation to confirm its efficacy and potential as a therapeutic agent. This hybrid *in-silico* approach contributes valuable insights to the design and discovery of novel drugs for cholangiocarcinoma treatment, laying the foundation for future experimental and clinical investigations.

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