



Original Research

Molecular Docking Analysis Reveals Potential Dual Targeting of FGFR4 and PI3K by Atorvastatin in Hepatocellular Carcinoma

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Abstract

Objectives: Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality worldwide. Despite the availability of systemic therapies, treatment resistance and tumor progression remain major challenges in HCC management. Increasing evidence indicates that aberrant activation of the fibroblast growth factor receptor 4 (FGFR4) axis and the phosphoinositide 3-kinase (PI3K) signaling pathway plays a critical role in hepatocarcinogenesis, tumor proliferation, and therapeutic resistance. Drug repositioning strategies offer an efficient approach for identifying new therapeutic applications for widely used non-oncologic drugs. This study aimed to investigate the potential inhibitory interactions of commonly prescribed drugs—atorvastatin, metformin, and celecoxib—against FGFR4 and PI3K α through molecular docking analysis and to compare their binding profiles with sorafenib, a reference drug used in HCC treatment.

Methods: The crystal structures of FGFR4 and PI3K α were retrieved from the Protein Data Bank and prepared using AutoDockTools. The three-dimensional structures of atorvastatin, metformin, celecoxib, and sorafenib were obtained from the PubChem database. Molecular docking simulations were performed using AutoDock 4 employing the Lamarckian Genetic Algorithm. The docking protocol was validated by redocking the co-crystallized ligand into the ATP-binding pocket, and root mean square deviation (RMSD) values below 2.0 Å were considered acceptable. Binding energies (ΔG), ligand–protein interaction profiles, and pharmacokinetic properties were analyzed using SwissADME.

Results: Docking simulations revealed that atorvastatin exhibited the strongest binding affinity toward both FGFR4 (-9.94 kcal/mol) and PI3K α (-9.10 kcal/mol), demonstrating binding energies comparable to or stronger than the reference inhibitor. Celecoxib also showed notable binding affinity toward PI3K α (-8.79 kcal/mol), whereas sorafenib demonstrated moderate binding interactions. In contrast, metformin exhibited relatively weak binding energies for both targets. Interaction analysis revealed that atorvastatin formed stabilizing hydrogen bonds and hydrophobic contacts with key residues within the ATP-binding pockets of FGFR4 and PI3K α . ADMET prediction indicated that all investigated compounds satisfied Lipinski's rule of five and displayed generally acceptable pharmacokinetic properties.

Conclusion: These findings suggest that atorvastatin may interact strongly with both FGFR4 and PI3K α signaling proteins, highlighting its potential as a dual-target modulator in hepatocellular carcinoma. The results provide preliminary *in silico* evidence supporting the repositioning of commonly prescribed drugs in HCC therapy, warranting further experimental and clinical validation.

Keywords: Hepatocellular carcinoma, FGFR4, PI3K, drug repositioning, molecular docking, Sorafenib

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Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer and continues to represent a substantial global health challenge.^[1] It ranks among the leading causes of cancer-related mortality worldwide, largely due to late diagnosis, rapid disease progression, and limited therapeutic options.^[2] Although several systemic therapies have been developed in recent years, the prognosis of advanced HCC remains poor, highlighting the need for novel therapeutic strategies and improved understanding of the molecular mechanisms underlying hepatocarcinogenesis. Among the molecular pathways involved in HCC development, the fibroblast growth factor receptor 4 (FGFR4) signaling axis has gained increasing attention.^[3] FGFR4 is predominantly expressed in hepatocytes and plays a crucial role in regulating hepatic metabolism, cell proliferation, and survival.^[4] Aberrant activation of the FGF19–FGFR4 pathway has been associated with tumor growth, angiogenesis, and poor clinical outcomes in HCC patients. Consequently, FGFR4 has emerged as a promising therapeutic target in liver cancer.^[5]

Another key signaling pathway implicated in hepatocellular carcinoma is the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway.^[6] Activation of the PI3K pathway contributes to tumor cell growth, metabolic alterations, and resistance to anticancer therapies.^[7] Mutations and over-activation of PIK3CA, the catalytic subunit of PI3K, have been reported in multiple cancers, including HCC, and contribute to tumor progression and therapeutic resistance. Drug repositioning has emerged as a promising strategy to identify new therapeutic applications for already approved drugs.^[8] Compared with conventional drug discovery, repositioning approaches offer significant advantages, including reduced development time, lower cost, and well-characterized pharmacokinetic and safety profiles. Increasing epidemiological and experimental evidence suggests that certain widely used drugs—such as statins, antidiabetic agents, and non-steroidal anti-inflammatory drugs—may influence cancer development and progression. For instance, statins have been associated with a reduced incidence of hepatocellular carcinoma in several observational studies,^[9] potentially through modulation of oncogenic signaling pathways. Similarly, metformin has demonstrated antitumor effects in multiple malignancies by influencing metabolic and PI3K-related pathways.^[10] Celecoxib, a selective cyclooxygenase-2 inhibitor, has also been reported to exert anticancer properties through anti-inflammatory and antiproliferative mechanisms.^[11] Despite these observations, the potential direct molecular interactions between these drugs and key signaling proteins involved in HCC progression remain incompletely understood. Computational approaches such as molecular

docking provide a valuable framework for investigating potential ligand–protein interactions and identifying novel inhibitory mechanisms.^[12,13]

Therefore, the present study aimed to evaluate the potential interactions of atorvastatin, metformin, and celecoxib with FGFR4 and PI3K using molecular docking analysis. Sorafenib, an approved multikinase inhibitor used in HCC treatment, was included as a reference compound to compare binding affinities and interaction profiles.

Methods

Protein Preparation

The three-dimensional crystal structures of fibroblast growth factor receptor 4 (FGFR4, UniProt ID: P22455) and phosphoinositide 3-kinase alpha (PI3K α , UniProt ID: P42336) were retrieved from the Protein Data Bank (PDB). The crystal structures with PDB IDs 5JKG for FGFR4 and 4FA6 for PI3K α were selected based on their structural resolution and suitability for molecular docking analysis. The structure 5JKG has a crystallographic resolution of 2.35 Å, whereas 4FA6 has a resolution of 2.70 Å. Protein preparation was performed using AutoDockTools (ADT, version 1.5.6).^[14] All crystallographic water molecules were removed from the protein structures, and polar hydrogen atoms were added. Kollman united atom charges were assigned to the protein structures. The co-crystallized ligands present in the crystal structures were extracted and saved separately for docking protocol validation. Additionally, electrostatic properties and solvation-related parameters of the proteins were evaluated using the Poisson–Boltzmann electrostatics server (<https://server.poissonboltzmann.org/>). This analysis was performed to characterize the electrostatic environment of the binding pockets prior to docking simulations. Finally, the prepared protein structures were converted into PDBQT format for subsequent docking calculations using AutoDock.

Ligand Preparation

The three-dimensional structures of atorvastatin, metformin, celecoxib, and sorafenib were retrieved from the PubChem database. Ligand structures were subjected to energy minimization prior to docking analysis. The ligands were prepared using AutoDockTools by assigning Gasteiger charges and defining rotatable bonds. All ligands were then converted into PDBQT format for docking simulations.

Docking Protocol Validation and Grid Definition

To ensure the reliability of the docking procedure, the docking protocol was validated by redocking the co-crystallized ligands into their respective binding pockets. The

ligands originally present in the crystal structures of FGFR4 and PI3K α were extracted and subsequently redocked using the same docking parameters applied for the docking simulations. The docking calculations were focused on the ATP-binding pocket of each protein. The predicted binding poses were compared with the experimentally observed ligand conformations obtained from the crystal structures. The accuracy of the docking protocol was assessed by calculating the root mean square deviation (RMSD) between the redocked ligand pose and the crystallographic ligand conformation. RMSD values below 2.0 Å were considered indicative of a reliable docking protocol. For docking simulations, grid maps were generated using AutoDockTools to cover the active binding sites of the target proteins. For FGFR4 (PDB ID: 5JKG), the grid box center coordinates were set to $x=-41.358$, $y=-16.614$, $z=377.853$, with grid dimensions of $50\times 48\times 44$ points along the x , y , and z axes, respectively. For PI3K α (PDB ID: 4FA6), the grid box center coordinates were defined as $x=44.481$, $y=14.981$, $z=31.276$, with grid dimensions of $50\times 40\times 38$ points along the x , y , and z axes. A grid spacing of 0.375 Å was applied in all docking calculations to ensure adequate coverage of the binding pockets while maintaining computational efficiency.

Molecular Docking

Docking calculations were performed using the AutoDock 4 platform with the Lamarckian Genetic Algorithm as the search method. Additionally, to ensure full reproducibility of the docking protocol, all relevant parameters were explicitly defined. The grid box center coordinates and dimensions for both FGFR4 and PI3K α were specified as described above. Each docking simulation was performed using 100 independent genetic algorithm runs, with a population size of 150, a maximum of 2,500,000 energy evaluations, and 27,000 generations. The mutation rate and crossover rate were set to the default AutoDock values of 0.02 and 0.80, respectively. All docking parameters were kept consistent across all ligand–protein complexes to ensure comparability of the results. The docking calculations were focused on the ATP-binding pockets of FGFR4 and PI3K α , as defined by the grid box parameters described above. For each ligand–protein complex, 100 independent docking runs were performed to ensure adequate sampling of possible binding conformations and to account for the stochastic nature of the Lamarckian Genetic Algorithm. The population size was set to 150 individuals, with a maximum number of 2,500,000 energy evaluations and 27,000 generations. All other docking parameters were maintained at their default AutoDock settings. To assess the reproducibility and stability of the docking results, the binding energies obtained from the 100 independent runs were analyzed,

and the mean binding energy along with the standard deviation (mean \pm SD) was calculated for each ligand–target complex.

Following the docking simulations, the resulting ligand conformations were clustered according to their positional similarity. The optimal binding pose for each ligand was selected based on the lowest predicted binding energy (ΔG) and the largest cluster size, which represents the most favorable and stable binding conformation.

Interaction Analysis

The molecular interactions between the docked ligands and the target proteins were analyzed to identify key binding features within the active sites. The best docking poses obtained from AutoDock were examined to determine hydrogen bonds, hydrophobic interactions, and other non-covalent interactions contributing to ligand binding stability. The ligand–protein interaction profiles were evaluated by analyzing contacts with amino acid residues located in the ATP-binding pockets of FGFR4 and PI3K α . Two-dimensional (2D) and three-dimensional (3D) interaction diagrams were generated to visualize the binding modes of the docked complexes and to identify key residues involved in ligand recognition.

ADMET (absorption, distribution, metabolism, excretion, and toxicity) Prediction

The pharmacokinetic and drug-likeness properties of the investigated compounds were evaluated using the SwissADME web server (<http://www.swissadme.ch>).¹⁵ The simplified molecular-input line-entry system (SMILES) structures of the ligands were retrieved from the PubChem database and used as input for the analysis. Several physicochemical and pharmacokinetic parameters relevant to drug development were assessed, including molecular weight (MW), lipophilicity (LogP), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), topological polar surface area (TPSA), and molar refractivity (MR). In addition, drug-likeness was evaluated according to Lipinski's rule of five. Predicted pharmacokinetic properties such as gastrointestinal (GI) absorption and blood–brain barrier (BBB) permeability were also analyzed to evaluate the suitability of the investigated molecules as potential drug candidates.

Statement on Ethics Committee Approval

This study was conducted entirely using *in silico* computational methods. No human participants, animal subjects, clinical data, or biological samples were used. All structural and chemical data were obtained from publicly available databases (Protein Data Bank and ChEMBL), which provide open-access and fully anonymized data. Therefore, ethics committee approval was not required for this study.

Results

Docking Protocol Validation

Docking protocol validation was performed by redocking the co-crystallized ligands into the ATP-binding pockets of FGFR4 and PI3K α using the same docking parameters applied in the study. The predicted binding poses were compared with the experimentally determined crystallographic conformations.

The redocking procedure yielded RMSD values of 1.22 Å for FGFR4 and 0.57 Å for PI3K α , both of which are well below the commonly accepted threshold of 2.0 Å. These results indicate excellent agreement between the predicted and experimental ligand conformations. The superposition of the crystallographic and redocked ligand conformations is shown in Figure 1, demonstrating a high degree of structural overlap and confirming the reliability of the docking protocol.

Binding Energy Analysis

The binding affinities of the investigated ligands toward FGFR4 and PI3K α were evaluated based on their predicted binding energies (ΔG) obtained from AutoDock simulations. The calculated docking scores are summarized in Table 1.

To evaluate the reproducibility of the docking simulations, mean binding energies and standard deviations were calculated from 100 independent runs for each ligand–protein complex. The relatively low variability observed across runs supports the consistency of the predicted docking outcomes.

FGFR4 Docking Results

For the FGFR4 target, atorvastatin demonstrated the strongest binding affinity with a docking energy of -9.94 kcal/mol, which was even lower than that of the reference inhibitor LY-2874455 (-9.55 kcal/mol). This finding suggests a strong predicted interaction of atorvastatin within the FGFR4 binding pocket. Among the other investigated compounds, sorafenib (-7.62 kcal/mol) and celecoxib (-7.43 kcal/mol) showed moderate binding affinities toward FGFR4. In contrast, metformin displayed the weakest interaction with a docking score of -5.16 kcal/mol, indicating relatively low binding affinity for the FGFR4 active site.

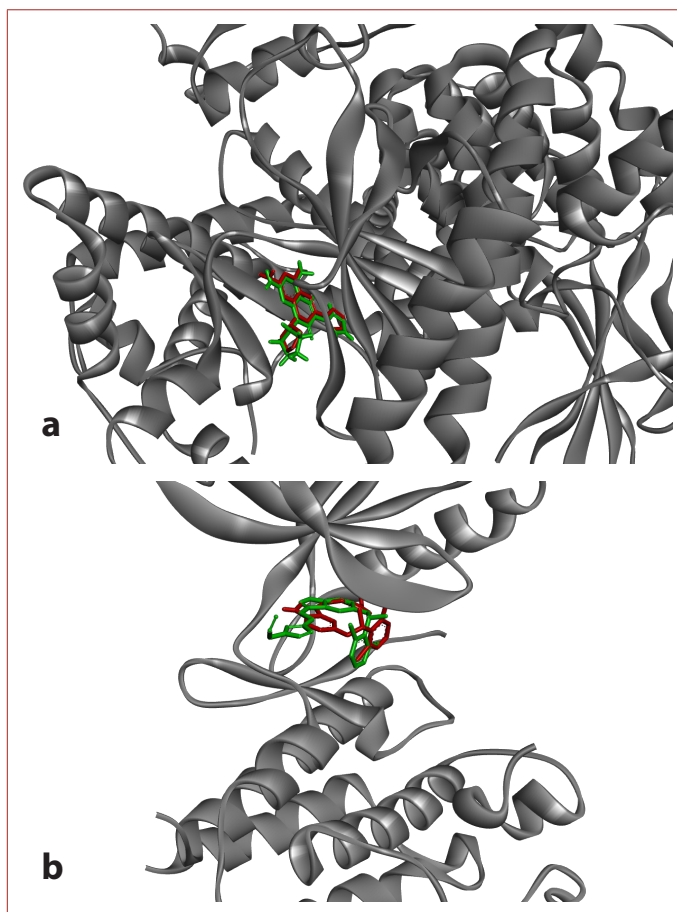


Figure 1. Docking protocol validation by redocking of co-crystallized ligands. **(a)** FGFR4 (PDB ID: 5JYG) and **(b)** PI3K α (PDB ID: 4FA6). The superposition of the native (crystallographic) and redocked ligand conformations demonstrates strong agreement, with RMSD values of 1.22 Å and 0.57 Å, respectively.

PI3K α Docking Results

Docking analysis against the PI3K α target revealed that atorvastatin also exhibited the strongest binding affinity among the tested compounds with a docking energy of -9.10 kcal/mol, followed by celecoxib (-8.79 kcal/mol). The reference ligand demonstrated a binding energy of -8.92 kcal/mol, indicating that atorvastatin displayed a comparable or slightly stronger predicted interaction with the

Table 1. Table 1. Best docking scores and mean binding energy values (\pm SD) obtained from 100 independent docking runs against FGFR4 and PI3K α

Ligand	FGFR4 (Best Score)	FGFR4 (Mean \pm SD)	PI3K α (Best Score)	PI3K α (Mean \pm SD)
Reference	-9.55	-8.341 \pm 0.431	-8.92	-8.803 \pm 0.065
Atorvastatin	-9.94	-9.5 \pm 0.3	-9.10	-8.8 \pm 0.2
Celecoxib	-7.43	-7.039 \pm 0.310	-8.79	-8.248 \pm 0.372
Sorafenib	-7.62	-7.248 \pm 0.373	-7.34	-6.822 \pm 0.284
Metformin	-5.16	-5.121 \pm 0.020	-4.7	-4.691 \pm 0.003

PI3K α binding pocket. Sorafenib showed a moderate binding affinity with a docking energy of -7.34 kcal/mol, while metformin again demonstrated the lowest binding affinity toward PI3K α with a docking score of -4.70 kcal/mol.

Overall, these findings indicate that atorvastatin exhibited the most favorable binding energies toward both FGFR4 and PI3K α , suggesting a potential interaction with key signaling proteins involved in hepatocellular carcinoma.

Interaction Analysis

To further elucidate the structural basis of ligand binding, detailed interaction analyses were performed for the docked complexes within the active sites of FGFR4 and PI3K α . Both two-dimensional (2D) interaction diagrams and three-dimensional (3D) binding pose visualizations were generated to characterize the molecular interactions. For FGFR4, atorvastatin exhibited a stable binding conformation within the ATP-binding pocket. The ligand formed a hydrogen bond with Arg483, which is located within the catalytic region of the kinase domain. In addition, multiple hydrophobic interactions were observed with key residues including Leu473, Val550, and Ala553, contributing to the stabilization of the ligand within the binding cavity. These residues are known to be involved in ligand recognition and kinase activity.

For PI3K α , atorvastatin also demonstrated a favorable binding orientation within the catalytic site. Hydrogen bond interactions were identified with Lys833 and Asp841, while hydrophobic contacts were observed with residues such as Met804, Ile831, and Tyr867. These interactions support a stable ligand–protein complex and suggest effective accommodation of the ligand within the active site. Although no prominent π – π stacking interactions were observed, the combination of hydrogen bonding and hydrophobic interactions appears to play a dominant role in stabilizing the ligand within both binding pockets.

The 2D interaction diagrams and 3D binding poses presented in Figures 2 and 3 further illustrate these interactions and provide visual confirmation of the ligand–protein binding modes.

- **(A)** Three-dimensional representation of atorvastatin docked in the FGFR4 active site, illustrating its orientation within the catalytic region.
- **(B)** Two-dimensional interaction diagram showing key ligand–protein interactions. Atorvastatin forms a hydrogen bond with Arg483, while hydrophobic interactions are observed with residues including Leu473, Val550, and Ala553. These interactions contribute to the stabilization of the ligand within the binding pocket.

Further analysis of the two-dimensional interaction diagram revealed that atorvastatin formed a hydrogen bond

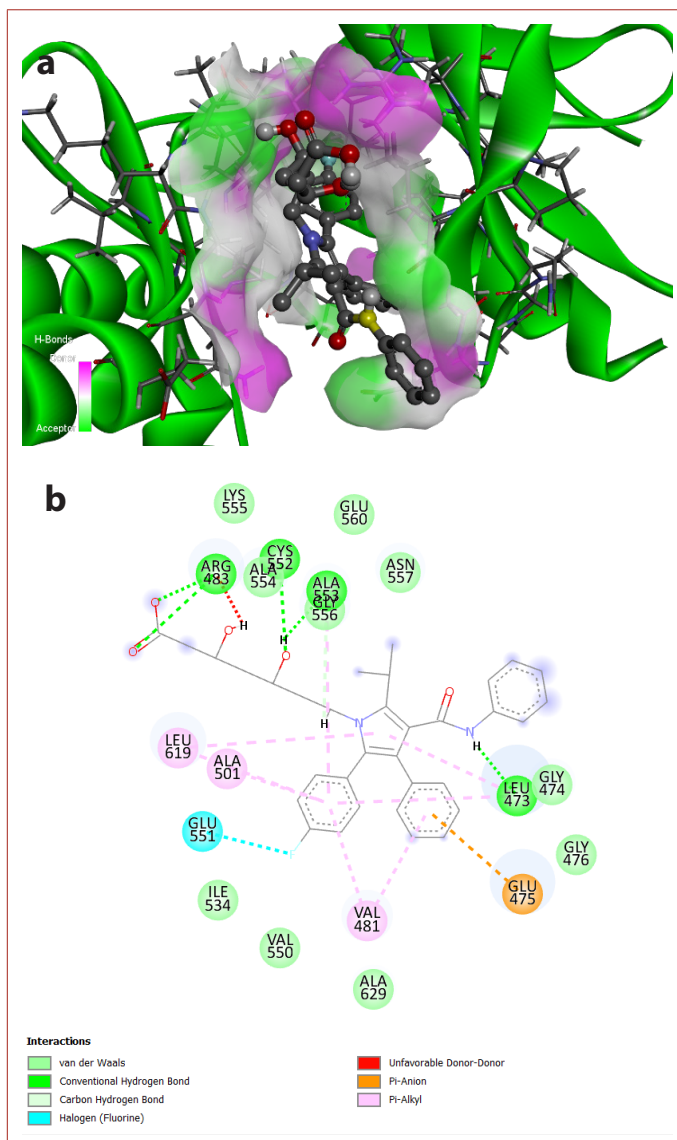


Figure 2. Interaction analysis of atorvastatin within the FGFR4 ATP-binding pocket.

with Arg483, while hydrophobic interactions were observed with residues such as Leu473, Val550, and Ala553 (Fig. 2b).

- **(A)** Three-dimensional visualization of atorvastatin positioned within the kinase active site, demonstrating its spatial orientation relative to surrounding residues.
- **(B)** Two-dimensional interaction diagram illustrating ligand–protein interactions. Atorvastatin forms hydrogen bonds with Lys833 and Asp841, along with hydrophobic contacts involving Met804, Ile831, and Tyr867, supporting stable binding within the catalytic pocket.

These residues are located within the ATP-binding region and are known to play a critical role in kinase activity. For PI3K α , atorvastatin also demonstrated a favorable binding orien-

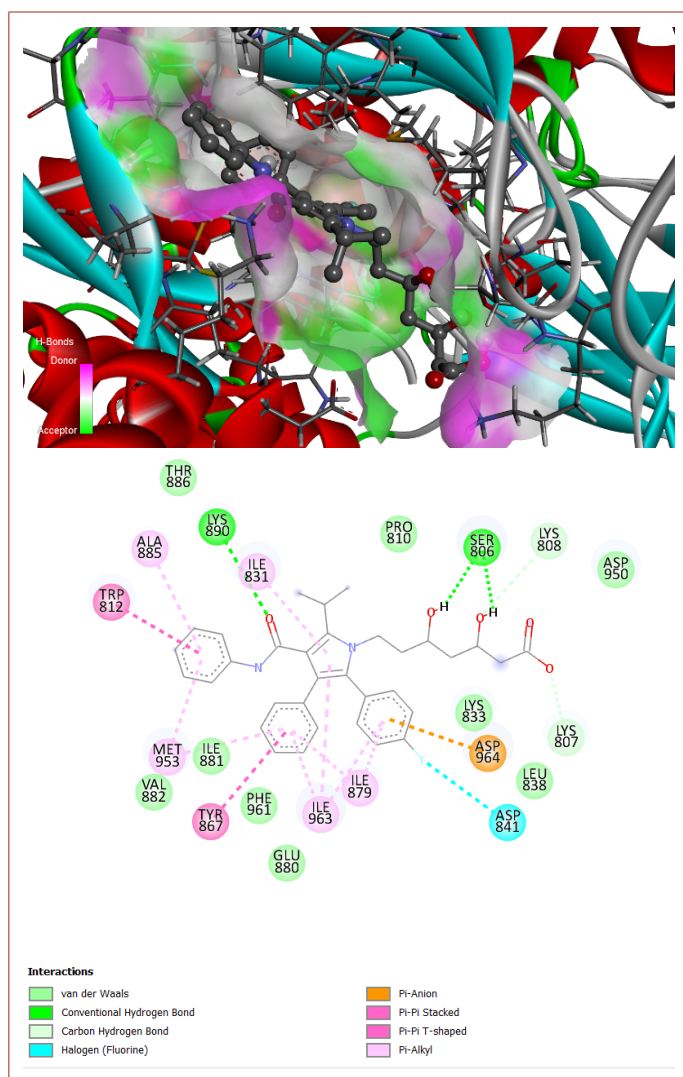


Figure 3. Interaction analysis of atorvastatin within the PI3K α catalytic binding pocket.

tation within the catalytic pocket of the kinase domain. The ligand formed stabilizing interactions with residues lining the active site, suggesting a strong and stable binding configuration (Fig. 3a). The two-dimensional interaction diagram further revealed hydrogen bonding and hydrophobic contacts between atorvastatin and surrounding residues within the PI3K α binding pocket (Fig. 3B). In particular, atorvastatin formed hydrogen bond interactions with Lys833 and Asp841, while additional hydrophobic contacts were observed with residues such as Met804, Ile831, and Tyr867, contributing to the stabilization of the ligand within the catalytic pocket.

ADMET Prediction

The predicted physicochemical and pharmacokinetic properties of the investigated ligands are presented in Table 2. All compounds satisfied Lipinski's rule of five, indicating acceptable drug-likeness profiles.

Among the investigated ligands, atorvastatin exhibited the highest molecular weight (558.64 g/mol) and the largest number of rotatable bonds (RB=13), suggesting greater molecular flexibility compared with the other compounds. In contrast, metformin showed the lowest molecular weight (129.16 g/mol) and fewer structural features, reflecting its smaller and more polar molecular structure. In terms of lipophilicity, the iLogP values ranged between 0.77 and 3.58, indicating moderate lipophilicity among the investigated ligands. Celecoxib demonstrated relatively balanced physicochemical parameters with moderate molecular weight, lipophilicity, and polar surface area. The TPSA values ranged from 86.36 to 111.79 Å², suggesting suitable polarity for potential oral bioavailability.

Regarding pharmacokinetic predictions, high gastrointestinal (GI) absorption was predicted for celecoxib and metformin, whereas atorvastatin and sorafenib were predicted to exhibit lower GI absorption. Additionally, none of the investigated compounds were predicted to cross the blood-brain barrier (BBB), indicating limited central nervous system penetration.

Overall, the ADMET analysis indicates that the investigated ligands possess generally acceptable physicochemical and pharmacokinetic properties according to the evaluated parameters.

Discussion

The present study investigated the potential interactions of commonly prescribed non-oncologic drugs with two key signaling proteins involved in hepatocellular carcinoma, FGFR4 and PI3K α , using molecular docking analysis. The results demonstrated that atorvastatin exhibited the most favorable binding affinities toward both targets, with docking energies comparable to or stronger than those of the reference inhibitor. Interaction analysis further revealed that atorvastatin formed stabilizing hydrogen bonds and hydrophobic contacts within the ATP-binding pockets of both FGFR4 and PI3K α . These findings suggest that atorvastatin may interact with critical residues located in the catalytic regions of these proteins and may potentially influence signaling pathways associated with HCC progression.

Aberrant activation of the FGFR4 signaling axis has been widely implicated in hepatocarcinogenesis, promoting tumor cell proliferation, survival, and resistance to therapy.^[3,5,16] Similarly, dysregulation of the PI3K/AKT signaling pathway plays a central role in tumor growth, metabolic reprogramming, and resistance to anticancer therapies in hepatocellular carcinoma.^[6,17] Targeting these signaling pathways has therefore emerged as an important therapeutic

Table 2. Physicochemical properties and ADME parameter values of ligands calculated with the SwissADME program

Properties name	Formula	MW (g/mol)	RB	HBA	HBD	iLogP	TPSA (Å ²)	MR	Lipinski rule	GI	BBBP
Reference (FGFR4)	C ₂₁ H ₁₉ C ₁₂ N ₅ O ₂	444.31	7	5	2	2.77	88.85	118.08	Yes	High	No
Reference (PI3Kα)	C ₁₆ H ₁₈ N ₆ O	310.35	2	4	2	1.82	102.48	89.13	Yes	High	No
Atorvastatin	C ₃₃ H ₃₅ FN ₂ O ₅	558.64	13	6	4	3.58	111.79	158.26	Yes	Low	No
Celecoxib	C ₁₇ H ₁₄ F ₃ N ₃ O ₂ S	381.37	4	7	1	2.56	86.36	89.96	Yes	High	No
Sorafenib	C ₂₁ H ₁₆ CF ₃ N ₄ O ₃	464.82	9	7	3	3.42	92.35	112.48	Yes	Low	No
Metformin	C ₄ H ₁₁ N ₅	129.16	3	2	4	0.77	88.99	36.93	Yes	High	No

MW: Molecular Weight; RB: Rotable Bond; HBA: H-Bond acceptor; HBD: H-bond donor; TPSA: Topological polar surface area; MR: Molar Refractivity; GI: Gastrointestinal absorption; BBBP: permeant. Ligands in bold indicate compounds that show better binding affinity than the reference ligand.

strategy in HCC management. The strong binding interactions of atorvastatin with both FGFR4 and PI3Kα observed in this study may indicate a potential modulatory effect on these oncogenic signaling pathways.

Accumulating evidence suggests that statins, particularly atorvastatin, may exert anticancer effects beyond their lipid-lowering properties. Several experimental and epidemiological studies have reported that statin use is associated with a reduced risk of hepatocellular carcinoma and improved clinical outcomes in patients with chronic liver disease.^[9,18] Proposed mechanisms include inhibition of tumor cell proliferation, induction of apoptosis, and suppression of oncogenic signaling pathways such as PI3K/AKT.^[19] In addition, statins have been reported to interfere with intracellular signaling cascades involved in tumor progression and angiogenesis. The binding interactions observed in the present docking analysis may provide a possible molecular explanation for these previously reported anticancer effects.

In addition to atorvastatin, celecoxib demonstrated relatively strong binding affinity toward PI3Kα in the present analysis. Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor that has been widely investigated for its anti-inflammatory and potential anticancer properties. Previous studies have suggested that COX-2 inhibition may suppress tumor growth, angiogenesis, and metastasis in several malignancies.^[20] The interaction of celecoxib with the PI3Kα binding pocket observed in this study may indicate a potential additional mechanism through which celecoxib could influence tumor-related signaling pathways.

As expected, sorafenib, a multi-kinase inhibitor commonly used in advanced hepatocellular carcinoma treatment, exhibited moderate binding interactions with the investigated targets. Sorafenib primarily acts by inhibiting multiple kinases involved in tumor proliferation and angiogenesis, including RAF kinases and vascular endothelial growth factor receptors.^[21] The docking results obtained in this study

are consistent with the known multi-target activity of sorafenib. In contrast, metformin demonstrated relatively weak binding affinities toward both FGFR4 and PI3Kα compared with the other investigated compounds. Although metformin has been reported to exert indirect anticancer effects through metabolic regulation and activation of the AMP-activated protein kinase (AMPK) pathway,^[10] the docking results suggest that its potential interactions with these specific kinase targets may be limited.

In addition to the docking results, the pharmacokinetic properties of the investigated compounds were evaluated using SwissADME, providing further insight into their potential drug-likeness and clinical applicability. All compounds satisfied Lipinski's rule of five, suggesting favorable oral drug-like characteristics. Atorvastatin exhibited relatively higher molecular weight and lipophilicity compared to the other compounds, which may influence its absorption and distribution properties. Although predicted gastrointestinal (GI) absorption was lower for atorvastatin and sorafenib, their established clinical use indicates that such limitations may be mitigated by formulation or dosing strategies. Celecoxib demonstrated balanced physicochemical properties, including moderate lipophilicity and high predicted GI absorption, supporting its suitability as an orally active compound. In contrast, metformin, despite its favorable GI absorption and low molecular weight, showed high polarity, which may limit its ability to interact strongly with hydrophobic binding pockets, consistent with its weaker docking performance. Overall, the ADME analysis suggests that the investigated compounds possess acceptable pharmacokinetic profiles, supporting their potential as candidates for further investigation in drug repositioning strategies.

The findings of the present study also highlight the potential value of drug repositioning strategies in identifying novel therapeutic candidates for hepatocellular carcinoma. Drug repositioning offers several advantages compared

with traditional drug development approaches, including reduced development time, lower costs, and the availability of well-established safety profiles.^[8] In this context, the strong binding interactions of atorvastatin with both FGFR4 and PI3K α suggest that widely prescribed metabolic drugs may interact with oncogenic signaling pathways involved in HCC progression. The low RMSD values obtained from redocking further support the accuracy and reliability of the docking protocol used in this study. Despite the promising findings obtained from the molecular docking analysis, several limitations should be acknowledged. First, the present study was based solely on in silico computational methods, and the predicted ligand–protein interactions require validation through in vitro biochemical assays and in vivo experimental studies. Furthermore, molecular docking provides a static representation of ligand binding and may not fully capture the dynamic nature of protein–ligand interactions under physiological conditions. Despite the promising findings obtained from the molecular docking analysis, several limitations should be acknowledged. First, the present study was based solely on in silico computational methods, and the predicted ligand–protein interactions require validation through in vitro biochemical assays and in vivo experimental studies. Furthermore, molecular docking provides a static representation of ligand binding and may not fully capture the dynamic nature of protein–ligand interactions under physiological conditions. Importantly, molecular docking represents a predictive computational approach and does not directly demonstrate biological activity or therapeutic efficacy. Therefore, the findings of this study should be interpreted as hypothesis-generating rather than confirmatory. Further validation through in vitro biochemical assays, cell-based studies, and in vivo models is necessary to confirm the functional and therapeutic relevance of these interactions.

Disclosures

Ethics Committee Approval: Ethics committee approval was not required for this study. This study was conducted entirely using in silico computational methods. No human participants, animal subjects, clinical data, or biological samples were used

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

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