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INTEGRATED VIRTUAL SCREENING AND ADMET EVALUATION OF IMIDAZOLE DERIVATIVES TARGETING GSK-3B AS POTENTIAL ANTICANCER AGENTS

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ABSTRACT:
Glycogen Synthase Kinase -3β (GSK-3β) is a multifunctional serine/ threonine protein kinase interfere in the regulation of cell proliferation, apoptosis, metabolism and multiple oncogenic signalling pathways. GSK-3β has been linked with progression of several human malignancies, making it protein target for anticancer drug discovery. In this present study aimed to find out newly designed imidazole derivatives (coded as IMD1–IMD5) as potential GSK-3β inhibitors using an integrated in silico drug discovery approach. In silico study evaluate that all five imidazole derivatives exhibited favourable binding affinities toward the catalytic pocket of GSK-3β, with docking scores from −8.09 to −8.88 kcal/mol. Among the evaluated compounds, IMD1 and IMD3 showed the highest binding affinity (−8.88 kcal/mol), followed by IMD4 (−8.58 kcal/mol), IMD2 (−8.17 kcal/mol), and IMD5 (−8.09 kcal/mol). Interaction analysis revealed that the ligands established multiple favourable contacts with critical active-site residues, including LYS85, MET101, VAL110, LEU132, TYR134, VAL135, CYS199, ASP200, PHE201, and LEU188, through hydrogen bonding, π–π stacking, π–alkyl, π–sigma, and hydrophobic interactions, indicating stable accommodation within the ATP-binding cavity. SwissADME analysis indicated that all derivatives complied with Lipinski's Rule of Five, exhibiting molecular weights below 500 Da, acceptable lipophilicity (LogP < 5), suitable TPSA values, and favourable hydrogen-bonding characteristics without significant drug-likeness violations. The compounds also evaluated promising oral bioavailability and physicochemical properties suitable for further optimization. These findings support the potential of this imidazole scaffold as a promising lead for the design of novel GSK-3β-targeted anticancer agents.

KEYWORDS: Imidazole derivatives, GSK-3β, Molecular docking, ADME properties, SwissADME; Target Protein–ligand interactions; Anticancer agents.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide. Approximately 20 million new cancer cases and 9.7 million cancer-related deaths were reported globally in 2022, and this burden is projected to continue rising with an ageing population, increasing urbanization, and a higher prevalence of lifestyle-associated risk factors (1, 2). Although advances in diagnostic technology and cancer biology have enabled the development of diverse therapeutic modalities, including surgery, chemotherapy, radiotherapy, and immunotherapy, most existing treatments remain limited by systemic toxicity, poor tumour selectivity, tumour heterogeneity, and the emergence of drug resistance (3). Consequently, there remains a pressing need for anticancer agents that act more selectively on cancer-driving molecular targets while minimizing adverse effects (4).

Protein kinases constitute a large family of regulatory enzymes that govern intracellular signal transduction through the reversible phosphorylation of substrate proteins, thereby controlling apoptosis, cell proliferation, metabolism, migration, and cell-cycle progression (5). Dysregulation of kinase activity, arising from genetic alterations or aberrant signalling, disrupts cellular homeostasis and contributes to malignant transformation; persistent activation of kinase-driven signalling promotes tumour growth, angiogenesis, invasion, metastasis, and resistance to anticancer therapy (6). Several oncogenic cascades, including the PI3K/Akt, MAPK, NF-κB, and Wnt/β-catenin pathways, are regulated by protein kinases and are frequently dysregulated in malignant cells (7). Protein kinases have therefore emerged as important druggable targets in oncology, and the development of selective kinase inhibitors continues to be a major focus of targeted cancer therapy (8).

Glycogen synthase kinase-3β (GSK-3β) is an abundantly expressed, constitutively active serine/threonine kinase that has attracted growing interest as an anticancer drug target because of its central role in numerous tumorigenic signalling networks (9, 10). It regulates cell-cycle progression, cellular proliferation, metabolism, differentiation, and apoptosis (11), and alterations in its expression or activity have been implicated in the initiation, progression, metastasis, and drug resistance of several human malignancies (10). GSK-3β also modulates key oncogenic pathways, including Wnt/β-catenin, PI3K/Akt, NF-κB, Hedgehog, and Notch signalling, underscoring its therapeutic relevance across a broad range of cancers (12). Consistent with this, elevated GSK-3β expression has been associated with significantly poorer overall survival in hepatocellular carcinoma, further underscoring its prognostic and therapeutic relevance in cancer (41).

Imidazole-based scaffolds have attracted considerable attention as kinase-targeting pharmacophores because of their structural versatility, synthetic accessibility, and favourable target-binding properties (13). The two nitrogen atoms within the imidazole ring facilitate hydrogen bonding and coordination-type interactions with active-site residues, enhancing binding affinity and target selectivity (13, 14). These properties have established the imidazole nucleus as an important pharmacophore in medicinal chemistry (15).

Imidazole derivatives display a broad spectrum of pharmacological activities and have been explored for infectious, inflammatory, and neoplastic diseases (16). In oncology specifically, structural modification of the imidazole scaffold has yielded derivatives capable of inhibiting tumour cell proliferation, inducing apoptosis, suppressing angiogenesis, and reducing metastatic potential (17). The structural flexibility of the imidazole ring further allows rational design of analogues with improved target selectivity and potency, making it a promising chemotype for the discovery of novel GSK-3β inhibitors with anticancer activity (18). Direct precedent exists for this chemotype–target combination: structurally optimized imidazole derivatives have been shown to inhibit GSK-3β with potent cytotoxicity across multiple cancer cell lines (42), and imidazole-pyridine hybrids docked against the GSK-3β ATP-binding site using the same crystal structure employed in the present study (PDB ID: 5K5N) have demonstrated favourable binding profiles, supporting the suitability of this structure for docking-based screening of imidazole derivatives (41).

Computer-aided drug design has become an integral component of modern drug discovery, owing to the growing availability of structural and biological data and the increasing computational power to process it (19, 20). Virtual screening enables the rapid evaluation of large compound libraries against a biological target, narrowing candidate selection prior to costly experimental testing (21), while molecular docking subsequently predicts the binding pose and estimates the binding affinity of individual compounds within the target active site (22). However, docking provides only a static, time-averaged view of the protein-ligand complex and does not capture the conformational flexibility of the system (21, 22). Molecular dynamics (MD) simulation addresses this limitation by modelling the time-dependent behaviour of the complex, including ligand mobility, conformational stability, and solvent effects, thereby providing a more complete assessment of binding stability (19, 23). Integrating virtual screening, molecular docking, and MD simulation into a single computational workflow allows candidate compounds to be prioritized on the basis of binding affinity, structural stability, and drug-likeness before committing to experimental validation, substantially reducing the time and cost associated with early-stage drug discovery (23, 24).

Favourable molecular recognition and complex stability alone do not guarantee the successful clinical development of a candidate compound; many promising leads fail during preclinical or clinical development because of unfavourable pharmacokinetics or unacceptable toxicity. Early in silico prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, together with established drug-likeness filters such as Lipinski's Rule of Five, therefore enables rapid triage of candidate molecules for favourable oral bioavailability and safety ahead of experimental evaluation, reducing late-stage attrition (25).

Although several computational studies have identified GSK-3β inhibitors from natural products or structurally diverse chemical libraries, imidazole-based derivatives have not been systematically investigated as GSK-3β-targeted anticancer agents, and few studies have combined virtual screening, molecular docking, and MD simulation within a single integrated workflow to evaluate their binding affinity, structural stability, and drug-likeness (26, 27).

Several recent studies support this integrated computational strategy. Li et al. highlighted protein kinases as attractive anticancer targets given their central role in regulating cell growth, survival, and metastasis, underscoring the value of developing selective kinase inhibitors, including GSK-3β inhibitors (28). Hua et al. applied virtual screening and molecular docking to identify GSK-3β inhibitor leads that occupied the ATP-binding site and remained stable throughout MD simulation (29). Murtazaeva et al. demonstrated that structural modification of the imidazole scaffold yields derivatives active against multiple cancer-related targets, including compounds capable of inhibiting proliferation, inducing apoptosis, suppressing angiogenesis, and limiting metastasis (30). Lam and Katritch discussed how structure-based computational approaches accelerate the identification and prioritization of kinase-targeted lead compounds (19). Hollingsworth and Dror further emphasized that combining molecular docking with MD simulation, which captures the dynamic behaviour of protein-ligand complexes over time, has become a standard component of structure-based drug discovery, including for GSK-3β inhibitors (31).

Building on this rationale, the present study employed an integrated in silico approach, comprising molecular docking and ADMET prediction, to design and evaluate a series of novel triphenyl-substituted imidazole derivatives (IMD1–IMD5) as potential GSK-3β inhibitors for anticancer drug discovery.

METHODOLOGY

2.1. Imidazole Derivatives

Heterocyclic compounds of Imidazole derivatives are well established class to known for their pharmacological and biological activities. Their development is supported by prior research emphasizing their promising anticancer potential and their capability to bind with essential amino acid residues of the major protease and glycogen synthase kinase-3 beta (GSK-3β), indicating their therapeutic effect(32). The synthesized compounds in this present study IMD 1 -IMD 5 are triphenyl substituted imidazole derivatives, chosen to assess the effect of the their biological activity and binding interactions(33, 34). The 2,4,5-triphenylimidazole core selected for IMD1–IMD5 has previously been synthesized via condensation of benzil, an aromatic aldehyde, and ammonium acetate, with substituted triphenylimidazole derivatives reported to possess notable antimicrobial and central nervous system activity, supporting the pharmacological relevance of this scaffold (43).

2.2. Ligand Preparation

The chemical structure of Imidazole derivatives IMD 1 to IMD 5 shown in fig 1 & are in form of SMILES were converted were converted into Structural Data File (SDF) format using the Open Babel software package(35, 36). The SDF generated file was later loaded into PyRx where they were further processing and analysis into PDBQT format through the Open Babel feature within PyRx. Before the docking process took place, the ligands were first minimized by the use of the Universal Force Field (UFF)(37, 38). The ligands were identified for molecular Docking studies. Docking study evaluated that all five compounds show binding affinities towards the target protein.

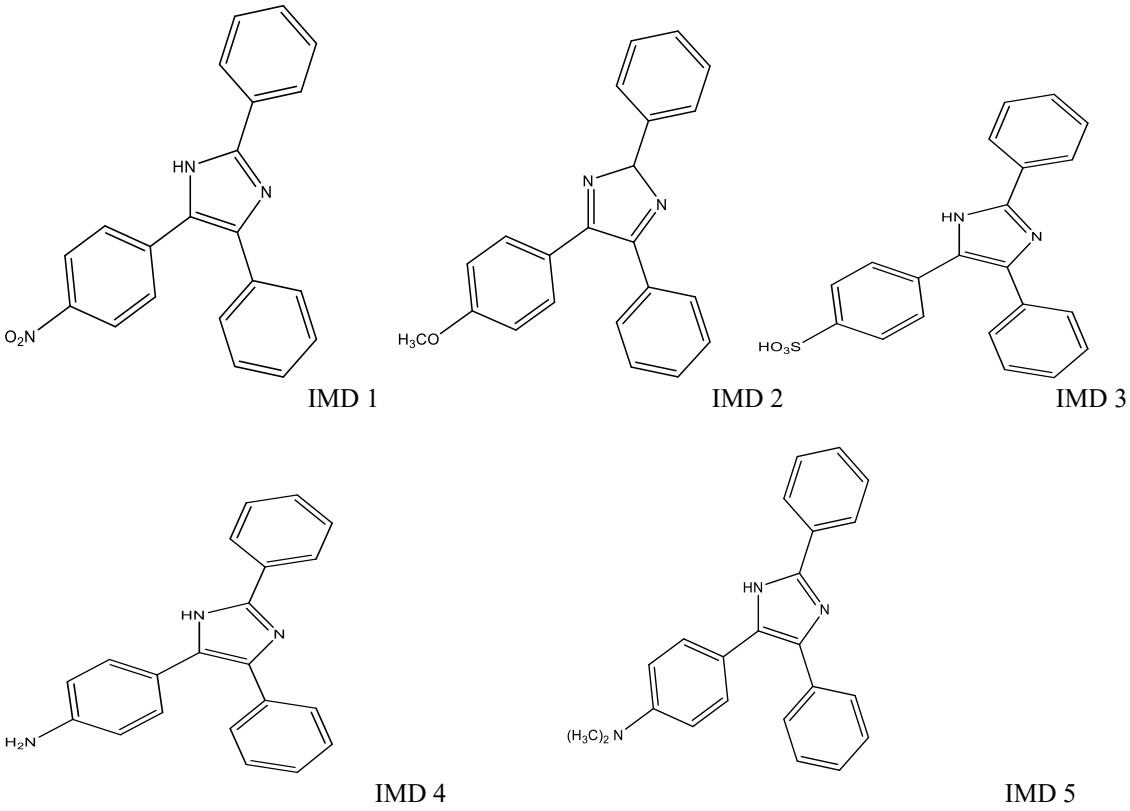

Figure 1. Chemical Structure of the imidazole derivatives (IMD 1 to IMD 5)

2.3. Protein Preparation

The Protein structure of glycogen synthase kinase-3 beta (GSK-3β; PDB ID: 5K5N) shown in fig 2 and was selected as the target protein for the molecular docking study. The three-dimensional structure was retrieved from the RCSB Protein Data Bank (PDB) repository. (https://www.rcsb.org/).

The identified Target protein structure was co-crystallized with the ligand K36, which served as the reference ligand for validating the docking protocol. Protein preparation was performed using the PyMOL molecular visualization software, where all non-essential components, including water molecules, ions, and the co-crystallized ligand located within the active binding site, were removed according to standard preparation procedures. The cleaned protein structure was subsequently imported into the PyRx platform for molecular docking analysis.

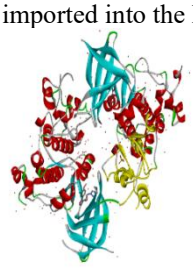

Fig 2 - Crystal structure of GSK-3beta

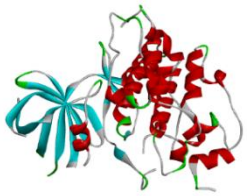

Fig 3 - Structure of edited 5K5N-Chain A ready for docking and further computational method.

2.4. Molecular Docking:

Molecular docking studies were carried out after preparation of the protein and ligand structures, using AutoDock Vina 1.1.2 integrated within the PyRx tool to predict binding affinity (39). Before docking, all ligand structures were converted into Protein Data Bank (PDB) and PDBQT format. A docking grid box was defined around the active binding site of GSK-3β, with dimensions of 1.35737 × 66.9738 × 58.6069 Å. The docking of the imidazole derivatives (IMD1-IMD5) was performed using identical grid box parameters to compare binding affinity and interaction pattern between

them. The resulting protein-ligand complex structures were subsequently analysed and visualized using BIOVIA Discovery Studio Visualizer to characterize hydrogen bonding, hydrophobic contacts, and other non-covalent interactions.

2.5. ADMET Prediction

The pharmacokinetic and toxicity profiles of the ligand compounds were evaluated through in silico ADMET analysis. Parameters related to absorption, distribution, metabolism, excretion, and toxicity (ADMET) were predicted using SwissADME (25) and the ADMETlab server (40). The obtained results were used to analyse the drug-likeness and pharmacokinetic properties of the compounds, providing insight into their potential suitability as therapeutic candidates.

3. RESULTS

3.1. Binding Affinities and Stability of Test Compounds with GSK 3 beta Drug Targets

Gibbs free energy of binding (ΔG kcal/mol) illustrated the variance of the binding affinities of these compounds. Shown by the results, Imidazoles had strong binding affinities, and therefore, the binding affinities of the remaining compounds were all found to be weaker. The remaining Imidazole compounds, IMD1, IMD3, IMD4 and IMD5, were characterized by the strongest binding affinities of all of the compounds analyzed. Their binding affinities were found to be -8.88, -8.88, -8.58, -8.17 and -8.09 kcal/mol, respectively. Remarkably, all the test compounds displayed binding affinities surpassing those of the standard inhibitors, as summarized in Table 1.

Table 1. The docking scores (ΔG in kcal/mol) of the test compounds against GSK-3Beta (5k5N)

Compound	Docking Score	Total intermolecular Binding Energy Kcal/mol	VDW_HB_ desolv Energy Kcal/mol	Electrostatic energy Kcal/mol
IMD 1	-8.88	-10.07	-9.77	0.30
IMD 2	-8.17	-9.36	-9.33	-0.03
IMD 3	-8.88	-9.69	-9.21	-0.48
IMD 4	-8.58	-9.66	-9.64	-0.02
IMD 5	-8.09	-9.28	-9.30	0.02

3.2. Molecular Docking Analysis of Selected Test Compounds

Figures 3–7 illustrate the three-dimensional (3D) binding conformations and two-dimensional (2D) interaction maps of the target protein GSK-3β (PDB ID: 5K5N) complexed with the five selected imidazole derivatives (IMD1–IMD5), which exhibited the highest binding affinities among the synthesized compounds. The molecular docking results demonstrated that all ligands occupied the ATP-binding pocket of GSK-3β and established multiple hydrophobic and aromatic interactions with the catalytic residues responsible for kinase inhibition.

IMD 1

Compound IMD 1 exhibited one of the highest docking affinities toward GSK-3β with a binding energy of −8.88 kcal/mol. The ligand was deeply accommodated within the ATP-binding pocket and established several favorable interactions with key amino acid residues (Figure 3). The aromatic rings of IMD1 formed π–alkyl interactions with VAL A:70, ALA A:83, LEU A:188, VAL A:110, LEU A:132, and LYS A:85, thereby stabilizing the ligand within the hydrophobic cavity. Furthermore, π–π T-shaped interactions were observed with PHE A:67, while π–sulphur interactions were established with MET A:101, contributing significantly to ligand stabilization. Carbon–hydrogen bonding was observed with ASP A:200 and TYR A:134, whereas additional van der Waals interactions involved ASN A:64, GLY A:65, ILE A:62, ASP A:133, GLU A:97, LEU A:130, PHE A:201, and ASN A:186. These interactions collectively indicate strong accommodation of IMD1 within the catalytic site of GSK-3β.

IMD2

Compound IMD2 demonstrates a docking score of −8.17 kcal/mol and fit the catalytic binding pocket of GSK-3β through broad hydrophobic interactions (Figure 4). The complex formed several π–alkyl interactions with residues like VAL A:70, VAL A:110, LEU A:130, LEU A:188, ALA A:83, and LYS A:85, which helped stabilize the ligand within the active site. Aadditionally π–sigma interaction with LEU A:132 further reinforced binding, while π–π stacking interactions with TYR A:134 added to aromatic stabilization. Carbon–hydrogen interactions involving ASP A:200 along with van der Waals contacts with GLU A:97, CYS A:199, PHE A:201, ASP A:133, VAL A:135, ASN A:64, and GLY A:63, all of which suggest that the ligand occupies the ATP-binding cavity quite stabilize.

IMD3

Compound IMD3 indicates with at the highest binding affinity (−8.88 kcal/mol) comparable to IMD1 and set up a dense network within the ATP-binding site of GSK-3β (Figure 5). The ligand exhibited prominent π–alkyl interactions with VAL A:70, ALA A:83, LEU A:188, LYS A:85, and LEU A:132, Additionally, it formed π-π T-shaped interactions were formed with PHE A:67. The two most interesting interactions are the two strong π–sulfur interactions with MET A:101 and CYS A:199 that enhanced the binding stability. Aalthough there was an unfavorable donor–donor interaction was observed near VAL A:135, it didn't significantly affect the overall binding affinity. On top of that, van der Waals

interactions with GLY A:63, GLY A:65, ASN A:64, TYR A:134, ASP A:133, ASP A:200, GLU A:97, PHE A:201, and ASN A:186 further stabilized the protein–ligand complex.

IMD4

Compound IMD4 achieved a docking score of −8.58 kcal/mol and forming a stable complex with GSK-3β by engaging in extensive aromatic interactions within the ATP-binding region (Figure 6). The ligand established π–alkyl interactions with VAL A:70, LEU A:132, LEU A:188, ALA A:83, and LYS A:85, along with π–sigma interactions involving CYS A:199. Additionally Hydrophobic interactions with PHE A:67 contributed to ligand stabilization, while van der Waals contacts were observed with ILE A:62, THR A:138, TYR A:140, ASP A:200, GLU A:97, LEU A:130, PHE A:201, GLN A:185, ASN A:186, and VAL A:135. All interactions shows that the ligand set up well within the kinase active site, even though it's binding affinity is gradually lower compared to IMD1 and IMD3.

IMD5

Compound IMD5 showed a docking score of −8.09 kcal/mol and interacted effectively with several key conserved residues within the ATP-binding pocket of GSK-3β (Figure 7). The ligand formed multiple π–alkyl interactions with VAL A:70, VAL A:110, LEU A:132, LEU A:188, ALA A:83, and LYS A:85, while π–sigma interactions were noted with CYS A:199. Notably, a strong π–sulfur interaction with MET A:101 helped stabilize the binding, and additional carbon- hydrogen interactions involved ASP A:200. Numerous van der Waals interact with GLU A:97, TYR A:134, VAL A:135, LEU A:130, PHE A:201, ASN A:64, ASN A:186, GLY A:65, and ILE A:62 help further to get stabilize by the ligand accommodation within the catalytic pocket.

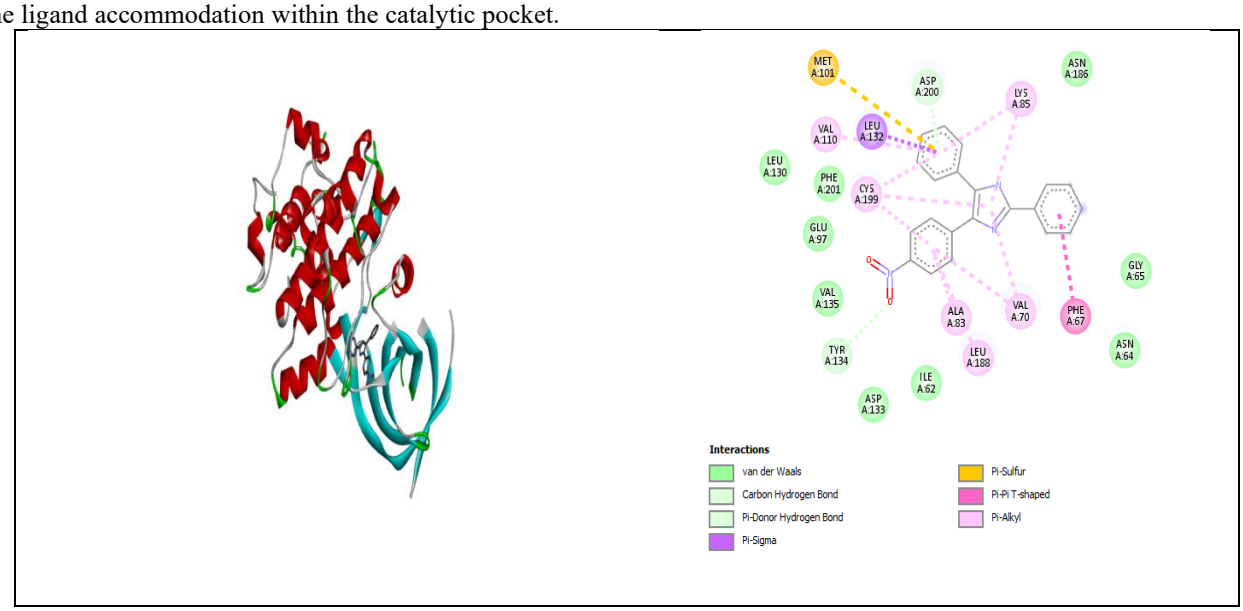

Figure 3. Shows Three-dimensional (right) and Two dimensional (left) views of how the amino acid residues of GSK-3β(5k5N) interact with Compound IMD 1.

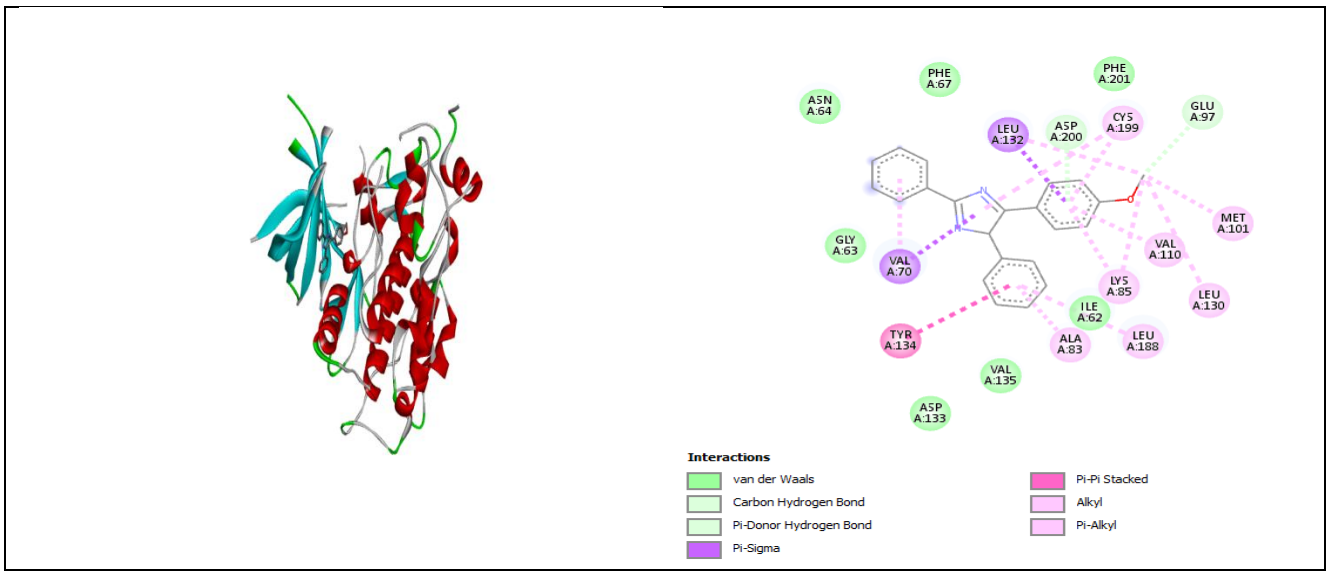

Figure 4. Three-dimensional (right) and Two dimensional left) views highlighting the molecular interactions of amino acid residues of GSK-3β(5k5N) and Compound IMD 2.

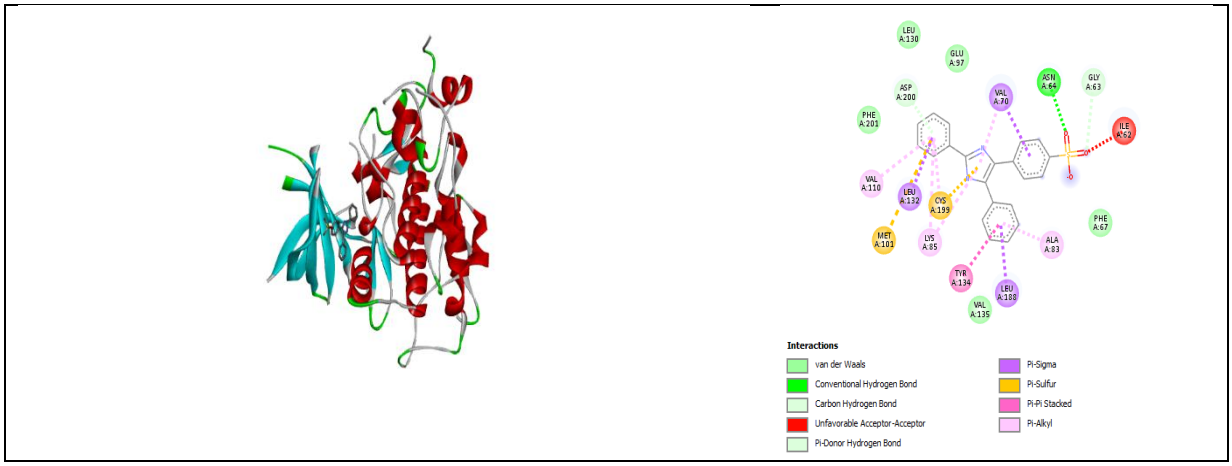

Figure 5 shows both Three-dimensional (right) and Two dimensional (left) views of the molecular interactions of amino acid residues of GSK-3β(5k5N) with Compound IMD 3.

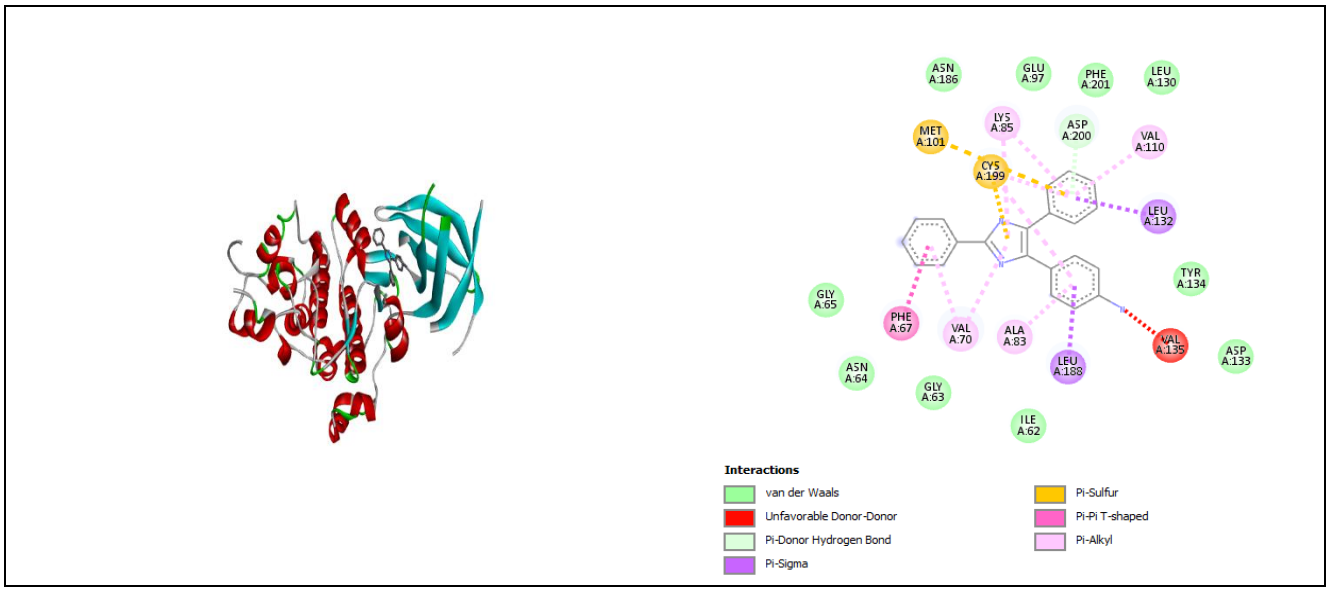

Figure 6 presents the Three-dimensional (right) and 2D (left) perspectives of these molecular interactions of amino acid residues of GSK-3β(5k5N) with Compound IMD 4

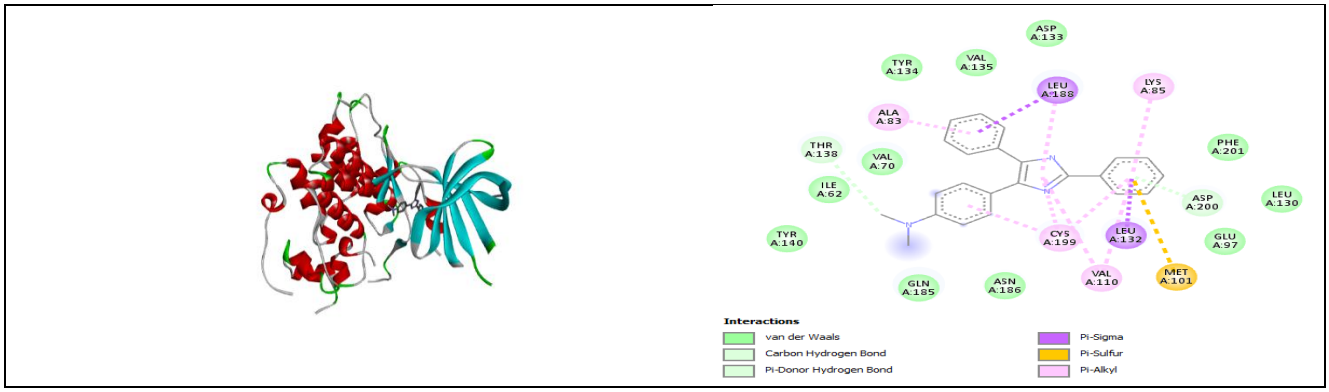

Figure 7 Three-dimensional (right) and Two dimensional (left) views of the molecular interactions of amino acid residues of GSK-3β(5k5N) with Compound IMD 5.

Overall, the molecular docking study showed that all five imidazole derivatives fit well into the ATP-binding pocket of GSK-3β. They created a range of favorable interactions including π–alkyl, π–π, π–sigma, π–sulfur, carbon–hydrogen, and van der Waals contacts with key catalytic residues like LYS85, MET101, VAL110, LEU132, TYR134, VAL135, CYS199, ASP200, PHE201, and LEU188. Within these compounds, IMD1 (A6) and IMD3 (A8) stood out by showing the strongest binding affinities (−8.88 kcal/mol), suggesting that these two derivatives could be the greatest potential as lead GSK-3β inhibitors for demonstration and experimental validation.

3.3. ADMET Profile

Table 2 summarizes the predicted molecular weight, lipophilicity, aqueous solubility, skin permeability, drug-likeness, gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate status, and

bioavailability score of IMD1–IMD5, as generated by SwissADME. Molecular weights ranged from 311.38 to 376.43 g/mol, with IMD3 showing the highest value (376.43 g/mol) and IMD4 the lowest (311.38 g/mol). The compounds displayed moderate to high lipophilicity, with consensus Log P values ranging from 4.17 (IMD3) to 4.94 (IMD5). Predicted aqueous solubility (Silicos-IT Log Sw) ranged from −8.87 to −8.08, indicating generally poor aqueous solubility across the series; IMD3 was predicted to be the most soluble (Log Sw = −8.08) and IMD5 the least soluble (Log Sw = −8.87). All five compounds satisfied Lipinski's Rule of Five and Veber's rule without violation, indicating favourable drug-likeness and oral-drug potential. Predicted skin permeability (Log Kp) ranged from −5.91 to −4.70, corresponding to moderate skin permeability overall, with IMD5 showing the highest predicted permeability (Log Kp = −4.70) and IMD3 the lowest (Log Kp = −5.91). All compounds were predicted to exhibit high GI absorption, consistent with favourable intestinal uptake following oral administration. Regarding BBB permeability, IMD2, IMD3, IMD4, and IMD5 were predicted to cross the BBB, whereas IMD1 was not. For P-gp substrate prediction, only IMD2 was classified as a likely P-gp substrate, while IMD1, IMD3, IMD4, and IMD5 were predicted to be non-substrates. All five compounds shared a bioavailability score of 0.55, indicating a moderate probability of oral bioavailability and supporting their potential as orally active drug candidates.

Table 2 Shows the Predicted lipophilicity (Log p), water solubility (Log Sw), drug-likeness, and bioavailability scores

Molecule	MW	Consensus Log P	Silicos-IT Log Sw	log Kp	Lipinski# Violations	Veber# Violations	Bioavailability Score	GI Absorption	BBB permeant	PgP Substrate
IMD1	341.36	4.34	-8.13	-4.92	0	0	0.55	High	No	No
IMD 2	326.39	4.49	-8.2	-5.15	0	0	0.55	High	yes	Yes
IMD 3	376.43	4.17	-8.08	-5.91	0	0	0.55	High	Yes	NO
IMD 4	311.38	4.42	-8.41	-5.1	0	0	0.55	High	Yes	No
IMD 5	339.43	4.94	-8.87	-4.7	0	0	0.55	High	Yes	No

4. DISCUSSION

Glycogen synthase kinase-3β (GSK-3β) is a versatile serine/threonine kinase that plays a central role in regulating cell proliferation, apoptosis, metabolism, and differentiation. Dysregulated GSK-3β activity has been linked to the initiation and progression of several human malignancies through its involvement in key oncogenic pathways, including Wnt/β-catenin, PI3K/Akt, NF-κB, Hedgehog, and Notch signalling. Targeting GSK-3β therefore represents an attractive strategy for the development of targeted anticancer therapies. Imidazole-containing compounds have attracted considerable attention in medicinal chemistry because of their structural flexibility, favourable physicochemical properties, and capacity to form multiple non-covalent interactions with protein kinases. With this rationale, the present study employed an integrated computational approach to evaluate a series of newly designed triphenyl-imidazole derivatives (IMD1–IMD5) as potential GSK-3β inhibitors. This approach is supported by prior evidence that structurally optimized imidazole derivatives can act as potent and selective GSK-3β inhibitors with cytotoxic activity across multiple cancer cell lines (42).

The molecular docking results showed that all five imidazole derivatives exhibited favourable binding affinity toward the ATP-binding pocket of GSK-3β, with docking scores ranging from −8.09 to −8.88 kcal/mol. IMD1 and IMD3 displayed the strongest binding affinity (−8.88 kcal/mol), followed by IMD4, IMD2, and IMD5. This strong binding affinity is likely attributable to the triphenyl-imidazole scaffold, whose extended aromatic framework enables efficient accommodation within the hydrophobic ATP-binding cavity. The multiple aromatic rings facilitate π-mediated interactions, while the imidazole nucleus contributes favourable electronic interactions with catalytically important residues. Structure–activity relationship analysis further suggests that electron-withdrawing substituents, particularly nitro and sulfonyl groups, enhance ligand binding through additional electrostatic interactions and improved complementarity with the active site, consistent with previous reports that appropriate substitution on the imidazole scaffold can significantly enhance kinase-inhibitory activity by strengthening hydrophobic and aromatic interactions within the catalytic pocket.

Analysis of protein–ligand interactions further supports the inhibitory potential of these compounds. All five derivatives formed multiple favourable contacts, including π–alkyl, π–π stacking, π–sigma, π–sulfur, carbon–hydrogen bonding, and van der Waals interactions, with critical residues including LYS85, MET101, VAL110, LEU132, TYR134, VAL135, CYS199, ASP200, PHE201, and LEU188. Among these, LYS85 and ASP200 are key residues within the ATP-binding region of GSK-3β, while MET101, CYS199, and PHE201 contribute substantially to ligand stabilization within the kinase pocket. The extensive hydrophobic interactions observed for IMD1 and IMD3 help explain their superior docking scores and indicate efficient accommodation within the catalytic cavity. The prominence of aromatic

interactions is particularly notable, as aromatic residues frequently mediate molecular recognition and stabilization of kinase inhibitors, thereby enhancing binding affinity and inhibitory potential.

The physicochemical and pharmacokinetic properties predicted by SwissADME further support the drug-likeness of the investigated compounds. All five derivatives satisfied Lipinski's Rule of Five and Veber's rule without violation, indicating favourable molecular properties for oral drug development. Their molecular weights remained below the recommended 500 Da threshold, and consensus Log P values ranging from 4.17 to 4.94 indicate a reasonable balance between lipophilicity and membrane permeability. Although all compounds were predicted to exhibit poor aqueous solubility, this behaviour is commonly observed among highly aromatic kinase inhibitors and may be addressed through pharmaceutical formulation or further structural optimization. Importantly, all compounds showed high gastrointestinal absorption together with a bioavailability score of 0.55, indicating promising oral absorption potential. Most derivatives were also predicted to cross the blood–brain barrier, while only IMD2 was flagged as a potential P-glycoprotein substrate, suggesting the remaining compounds may be less susceptible to P-gp-mediated efflux.

The observed differences in docking affinity among the derivatives appear closely associated with the nature and position of substituents on the triphenyl-imidazole scaffold. IMD1 and IMD3, which exhibited the strongest binding affinities, contain electron-withdrawing groups capable of enhancing electrostatic interactions while maintaining strong hydrophobic contacts within the ATP-binding site. In contrast, derivatives with comparatively lower docking scores may possess substituents that provide fewer stabilizing interactions or introduce steric hindrance that limits optimal accommodation within the catalytic pocket. These observations are consistent with established structure–activity relationships reported for GSK-3β inhibitors, in which an appropriate balance of hydrophobic aromatic fragments and hydrogen-bond-forming functional groups is essential for achieving high binding affinity and selectivity.

Overall, this computational study indicates that the designed triphenyl-imidazole derivatives possess promising characteristics as potential GSK-3β inhibitors. The combination of favourable docking scores, strong interactions with key catalytic residues, good drug-likeness, and promising pharmacokinetic profiles supports their potential as lead candidates for further development, with IMD1 and IMD3 emerging as the most promising molecules based on their higher binding affinity and favourable interaction patterns. Nonetheless, molecular docking provides only a static snapshot of protein–ligand binding and cannot fully capture the dynamic behaviour of these complexes under physiological conditions. Further validation through molecular dynamics simulation, MM-GBSA binding free-energy calculations, and in vitro and in vivo experimental evaluation will therefore be required to confirm the stability, inhibitory activity, and overall therapeutic potential of these compounds as GSK-3β-targeted anticancer agents.

CONCLUSIONS

In the current study, in-silico drug discovery technique was used to examine a set of novel triphenyl-imidazole derivatives (IMD1-IMD5) as prospective GSK-3β inhibitors in cancer treatment. In terms of molecular docking study, it is evident that all the tested compounds have good binding affinity to the ATP-binding region of GSK-3β, with IMD1 and IMD3 having the highest binding affinity (−8.88 kcal/mol). Based on the interaction study, the compounds form multiple hydrophobic, aromatic and hydrogen bonding with the residues at the catalytic site.

Additionally, the SwissADME prediction further showed that all the derivatives have favorable pharmacological properties by satisfying both the Lipinski's and Veber's rules without any breach. The derivatives had appropriate lipophilicity, good predicted GI absorption, moderate oral bioavailability, and promising pharmacokinetic properties except that the predicted aqueous solubility is relatively low for the derivatives. SAR analysis indicated that the presence of electron-withdrawing groups such as nitro and sulfonyl groups improves the binding ability of the derivatives to GSK-3β catalytic site.

Overall, the results from the analysis of molecular docking and pharmacokinetics show that the studied triphenyl-imidazole derivatives are promising leads for developing novel anticancer drugs that target GSK-3β. From the analysed drugs, IMD1 and IMD3 proved to be the most promising molecules. However, it is worth noting that the results of the study are computational-based predictions only. Consequently, in order to validate the stability and biological activity of these drugs, molecular dynamics, binding free energy using MM-GBSA, inhibition enzyme tests, and anticancer in vitro experiments should be performed.

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