Biological and Biomedical Journal

Journal homepage: https://bbj.journals.ekb.eg

Computational prediction and QSAR-based design of novel curcumin derivatives: Enhancing insulin receptor binding and pharmacokinetic properties for improving therapeutic efficacy

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ARTICLE INFO

Received: 21/2/2025
Revised: 15/5/2025
Accepted: 3/6/2025

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P-ISSN: 2974-4334
E-ISSN: 2974-4324
DOI:
10.21608/BBJ.2025.361161.1089

ABSTRACT

Curcumin (CUR) demonstrates therapeutic potential for insulin resistance (IR) and type 2 diabetes through anti-inflammatory and insulin-sensitizing properties. However, clinical applications remains limited due to poor bioavailability and weak insulin receptor binding affinity. Despite extensive anti-diabetic studies, a critical gap exists in developing structurally optimized CUR-derivatives with enhanced insulin receptor binding and validated pharmacokinetic profiles. This study aims to design novel CUR-derivatives with improved insulin receptor interactions using integrated computational approaches. A comprehensive framework combining molecular docking, QSAR modelling, and ADMET profiling evaluated ten CUR-derivatives. Molecular docking simulations against insulin (PDB ID: 6JK8) and insulin receptor (PDB ID: 4ZXB) used AutoDock Vina, with genetic algorithm-based optimization guiding rational design. CUR-Derivatives demonstrated substantially improved binding affinities versus native CUR:-7.16 to -9.98 kcal/mol (insulin) and -7.86 to -10.49 kcal/mol (insulin receptor) compared to -6.81 and -5.03 kcal/mol, respectively. CUR-3 emerged as the lead candidate with superior binding affinity (-9.98/-10.49 kcal/mol), balanced ADMET properties (LogP = 3.876, LogS = -3.729), and favorable safety profile. QSAR analysis ($R^2 \approx 1$, $Q^2 = 0.75$) identified moderate lipophilicity and balanced hydrogen bonding as critical activity determinants.CUR-3 represents a promising scaffold for anti-diabetic therapeutics requiring experimental validation to confirm therapeutic potential for IR management.

Keywords: Anti-diabetes, Curcumin, Insulin receptor, Insulin resistance

1. Introduction

Curcumin (CUR), a natural polyphenolic compound, has shown promising potential as an insulin receptor inhibitor in the treatment of insulin-resistant (IR) disorders such as type 2 diabetes mellitus (T2-DM), obesity, and non-alcoholic fatty liver disease (NAFLD). Its therapeutic applications are primarily attributed to its anti-inflammatory, antioxidant, and insulin-sensitizing properties (Salzedas et al., 2020). CUR's efficacy in improving insulin resistance and related metabolic parameters has been demonstrated in both preclinical and clinical studies

In a murine model of T2-DM, CUR-loaded liposomes significantly improved glucose metabolism and IR likely due to reduced liver inflammation and oxidative stress (Zhang et al., 2021; Mahdavi et al., 2021; Li et al., 2024). It has been reported that CUR supplementation led to a notable decrease in fasting blood glucose and hemoglobin A1c levels, indicating improved glycemic control (Prabowo et al., 2023). CUR may enhance incretin secretion and inhibit digestive enzymes, which collectively contribute

to lower blood glucose levels (Prabowo et al., 2023). Additionally, CUR's anti-inflammatory properties may play a role in improving insulin sensitivity, further aiding glucose metabolism (Panda, A et al., 2017). Nano-CUR improves pancreatic β-cell function and increased the gene expression of insulin and insulin receptors in diabetic rats, indicating its potential to enhance insulin sensitivity (Weisberg et al., 2016; Gouda et al., 2019). In clinical trials, patients who supplemented with CUR over extended periods (≥12 weeks) exhibited significant reductions in glycemic indices, reinforcing its potential as a therapeutic agent for T2-DM, obesity, and NAFLD (Mahdavi et al., 2021; Zeng et al., 2023; Asghari et al., 2024). CUR's anti-inflammatory effects are evidenced by its ability to lower inflammatory markers such as tumor necrosis factor-α (TNF-α) and interleukine -6 (IL-6), which is elevated in IR states (Li et al., 2024).

It also enhances antioxidant defenses by increasing hepatic glutathione and superoxide dismutase (SOD) activities, contributing to improved insulin sensitivity (Li et al., 2024). Antidiabetic therapies, such as metformin and insulin, do not face the same bioavailability challenges as CUR, making them more reliable in clinical settings. While CUR-derivatives show potential, their clinical applicability is still limited by the need for more human studies to confirm efficacy and safety (Ataei et al., 2023). Despite the promising strategies to enhance CUR's bioavailability, the clinical applicability of CUR-derivatives remains constrained by the need for further research and validation in human trials. Studies indicate that CUR and its metabolite tetrahydrocurcumin improve insulin receptor binding in erythrocytes, suggesting a complex interaction with receptor dynamics (Murugan et al., 2008).

CUR's poor aqueous solubility due to these pharmacokinetic barriers and rapid systemic elimination result in low bioavailability, which limits its therapeutic efficacy in diabetes management (Vasile et al., 2024; Chelimela et al., 2024) necessitating alternative approaches to improve absorption and retention (Popović et al., 2024). One of strategies to enhance bioavailability was development of monocarbonyl analogues of CUR (MACs) and other chemical modifications have shown promise in improving bioavailability and pharmacological activity (Vasile et al., 2024). The development of MACs aims to enhance bioavailability and pharmacological activities, presenting a promising alternative to conventional treatments while addressing these limitations. Nanotechnological advances, such as nanofibers, nanoparticles, and nanoemulsions, have been employed to enhance CUR's solubility and absorption, leading to improved antidiabetic effects in preclinical studies (Ataei et al., 2023). Novel drug delivery systems, including micelles, liposomes, and solid lipid nanoparticles have been explored to enhance CUR's pharmacokinetic profile without altering its pharmacodynamics (Chelimela et al., 2024). However, despite its promising biological activities, CUR exhibits limited clinical applicability due to its weak binding affinity to insulin receptors and unfavorable pharmacokinetic properties.

The research gap is clear in the lack of structurally optimized CUR-derivatives with validated pharmacokinetics would strengthen this section. These challenges necessitate the development of novel CUR-derivatives with enhanced insulin receptor binding and optimized pharmacokinetics to improve its therapeutic efficacy. Recent advancements in computational drug design, particularly molecular modeling and docking simulations, have facilitated the rational design of CUR-analogs with improved receptor interactions. Molecular dynamics simulations and quantitative structure-activity relationship (QSAR) analyses provide insights into the structural modifications that enhance CUR's binding affinity to the insulin receptor, potentially leading to improved insulin sensitivity and metabolic regulation. This study explores recent advancements in the prediction and design of new powerful series of CUR-derivatives as part of research into the synthesis of novel heterocycles and their molecular docking prediction with improved insulin receptor binding and pharmacokinetic properties. By integrating molecular modeling techniques and innovative drug delivery strategies, the development of CUR-based therapeutics may offer a promising approach to managing insulin resistance and related metabolic disorders.

Methodology

Preparation of the protein

The X-ray crystallographic 3D structural segments of insulin (PDB ID: 6JK8) and IR (PDB ID: 4ZXB) were downloaded from the Protein Data Bank (PDB), which is kept up to date by the Research Collaborator for Structural Bioinformatics (RCSB) (Berman et al., 2000). CB-DOCK2 was used to validate the predicted binding site for this protein, which was based on information from the literature (Liu et al., 2022). To prepare the protein for docking, polar hydrogens were added, water molecules were eliminated, and Gasteiger charges were assigned using AutoDock Tools 1.5.7 (Morris et al., 2009).

Ligands generation and preparation

CUR derivatives given in Table 1 were sketched with ChemDraw Professional. The generated ligands underwent optimization using Avogadro 1.2.0, an advanced molecular editor and visualization tool (Hanwell et al., 2012). Ligand structures were prepared and refined using the MMFF94 force field to ensure proper geometric configurations and minimal potential energy, thereby enhancing their suitability for subsequent virtual screening. To facilitate further processing, Open Babel online was utilized to convert the SDF format files into the PDB format.

Virtual screening by molecular docking

AutoDock vina, a well-known molecular docking program renowned for its effectiveness and precision in forecasting ligand-protein interactions, was used to screen ligands with a high affinity for the enzyme's binding site to find possible candidates against insulin and insulin receptors. To direct the docking simulations, a grid box was established around the anticipated active site coordinates derived from CB-Dock2. For every ligand, several docking runs were conducted to investigate various binding orientations and conformations inside the active site. Ligands were validated using KDeep Server and ranked according to their binding affinity scores (ΔG) (Jiménez et al., 2018).

Visualization

BIOVIA Discovery Studio 2020 (Dassault Systèmes BIOVIA, 2020) was used to visualize and study the binding modalities and interactions of top-ranking ligands with specific proteins. This software offered comprehensive information on the particular binding interactions that support the stability and effectiveness of the ligand-protein complexes, such as hydrogen bonds, hydrophobic contacts, and π-π stacking interactions.

In silico physico-chemical parameters

To anticipate their drug similarity and ADMET qualities, the compounds that were chosen after molecular docking were subjected to additional study. Drug development relies heavily on ADMET, which stands for absorption, distribution, metabolism, excretion, and toxicity. It assesses the how a medication interacts with the body. The online web-server SwissADME (http://www.swissadme.ch), ADMETlab 2.0, pkCSM, and ADMET SAR were used to assess the drug-likeness and ADMET characteristics. Their pharmacokinetic and physicochemical characteristics were assessed using the ADMET Lab 2.0 (https://admetmesh.scbdd.com). The compounds' drug-likeness was assessed using Lipinski's RO5, which states that the molecules' molecular weight (MW) must be less than 500 Da, their logP must be less than 5, and their number of hydrogen bond acceptors (HBA) and donors must be less than 10 (Diana et al., 2017).

Quantitative structure-activity relationship analysis

Molecular descriptors were calculated and utilized as independent variables in the QSAR model, which was constructed using multiple linear regression analysis and machine learning algorithms. The model's predictive performance was assessed based on standard statistical parameters. The docked compounds underwent Quantitative Structure-Activity Relationship (QSAR) analysis using specialized software (ChemMaster), with biological activity—represented by Gibbs free energy of binding—serving as the dependent variable. To ensure the model's robustness and applicability to novel compounds, both internal and external validations were performed.

Molecular docking

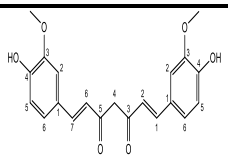
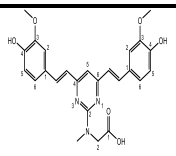
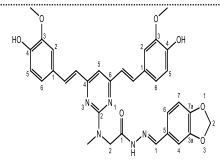
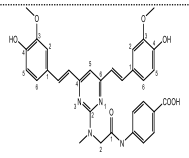
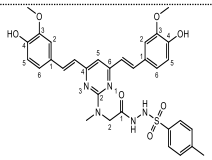
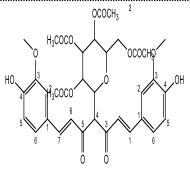
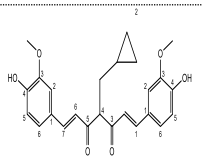
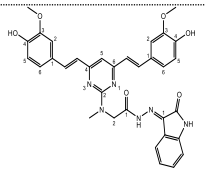
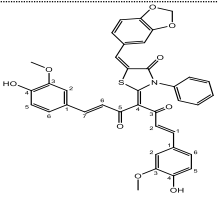
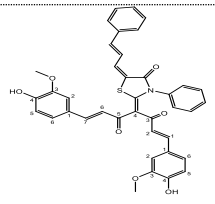
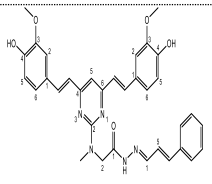
Curcumin (969516) was used as a reference compound to evaluate the accuracy and reliability of the docking simulations. Molecular docking was employed using MGL tools (AutoDock 1.5.7) to investigate the interactions

between the CUR and CUR-derivatives (Cur-1/Cur-10) with insulin and IR.

The role of the genetic algorithm

Genetic algorithm (GA)-based heuristic was employed to guide the fragment-based optimization of the CUR-scaffold. In this approach, molecular fragments were treated as genes, and their attachment positions were encoded into chromosomes. An initial population of CUR-derivatives was generated by random fragment substitution. Fitness of each derivative was evaluated based on molecular docking scores against 4ZXB and 6KJ8, combined with key ADMET predictions. The GA then applied selection, crossover, and mutation operators over multiple generations to evolve high-affinity, drug-like candidates.This heuristic enabled efficient exploration of chemically diverse derivatives while prioritizing bioactivity and favorable pharmacokinetics.

Table 1. The structural modifications of CUR molecule to generate ten derivatives (CUR-1 to CUR-10)

Ligands	Chemical Structure	Ligands	Chemical Structure
CUR		CUR-1	
CUR-2		CUR-3	
CUR-4		CUR-5	
CUR-6		CUR-7	
CUR-8		CUR-9	
CUR-10			

Result

Molecular docking analysis of CUR-derivatives

The molecular docking simulations reveal significant binding interactions between CUR-derivatives and both insulin and IR structures. Among all tested compounds, Cur-3 demonstrated superior binding affinity to both targets, suggesting its potential as a lead compound for insulin-related therapies. The binding analysis of CUR-derivatives with insulin shows that CUR-3 exhibits the strongest binding affinity (-9.98 kcal/mol), followed closely by CUR-2 (-9.91 kcal/mol) and CUR-9 (-9.49 kcal/mol). All derivatives demonstrated substantially improved binding compared to the reference CUR compound

The interaction analysis with insulin receptor demonstrates CUR-3's exceptional binding affinity (-10.49 kcal/mol), which is significantly stronger than the reference CUR (-5.03 kcal/mol). CUR-9 (-9.58 kcal/mol) and CUR-8 (-9.43 kcal/mol) also showed promising results, indicating their potential as insulin receptor modulators.

Table 3. provides The insulin receptor binding data which suggest that even more dramatic improvements, with CUR-03 achieving -10.49 kcal/mol binding energy—a remarkable 108% enhancement over CUR (-5.03 kcal/mol). This substantial improvement suggests that the structural modifications are particularly well-suited for insulin receptor interactions. The correlation between high binding affinity and elevated Pic50/Pkd values across derivatives supports their potential as insulin receptor modulators with enhanced therapeutic efficacy.

Binding mode analysis

The molecular docking results revealed specific binding interactions between selected CUR-derivatives and the target proteins. The most promising compounds (CUR-2, CUR-3, and CUR-9) demonstrated diverse and stable interactions with key amino acid residues in both insulin and insulin receptor binding sites.

Figure 1. The 2D and 3D interaction diagrams provide crucial mechanistic insights into the binding modes of selected compounds with insulin. The visual analysis reveals that CUR-2, CUR-3, and CUR-9 establish more extensive and diverse interaction networks compared to native CUR, including conventional hydrogen bonds, carbon-hydrogen bonds, and hydrophobic interactions.

Figure 2A. Interaction profiles highlight the superior binding characteristics of the derivatives with the insulin receptor. CUR-3 shows particularly favorable interactions with key residues including LYS310, GLY359, PRO307, CYS304, CYS308, and LEU360 through multiple interaction types. The comprehensive binding network formed by these derivatives, compared to the limited interactions of native curcumin, provides molecular-level justification for their enhanced binding affinities and potential

ADMET properties analysis

Assessment of the drug-likeness and ADMET (Absorption, distribution, metabolism, excretion, and toxicity) properties of CUR-derivatives provides crucial information regarding their pharmacokinetic behaviors and potential therapeutic applications. Figure (3) shows that among the derivatives, CUR-3 demonstrates the most balanced ADMET profile with moderate lipophilicity, acceptable solubility, reasonable metabolic stability, and lower clearance than the reference compound. While CUR-9 shows excellent absorption properties, its high CYP inhibition potential and higher plasma protein binding may limit its therapeutic window. CUR-2, despite good binding affinity, has suboptimal solubility and absorption characteristics. Table 4ADMET analysis quantifies the pharmacokinetic advantages of the derivatives. CUR-03 emerges as the most balanced candidate with moderate lipophilicity (LogP = 3.876), acceptable solubility (LogS = -3.729), and favorable metabolic profile with low CYP inhibition. The data reveals critical insights: while CUR-09 shows superior absorption (HIA = 0.926), it’s very high CYP inhibition and poor solubility limit clinical applicability. The half-life and clearance data support CUR-3's potential for sustained therapeutic effects with convenient dosing intervals.

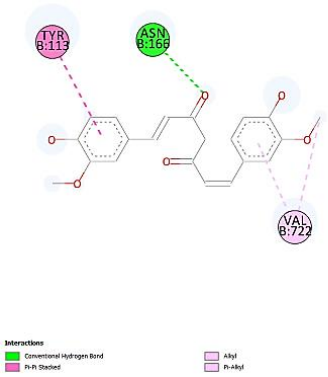
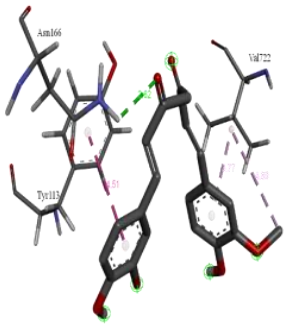
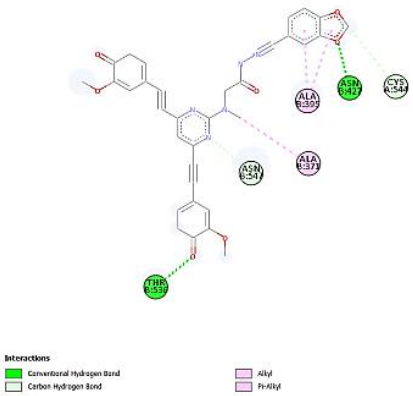
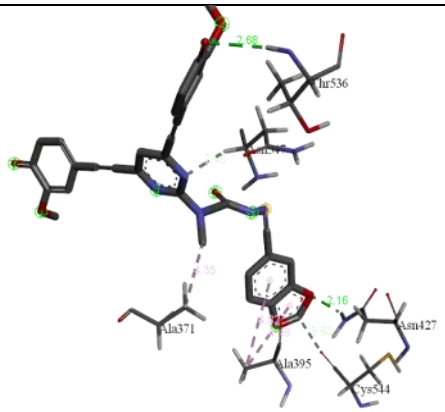
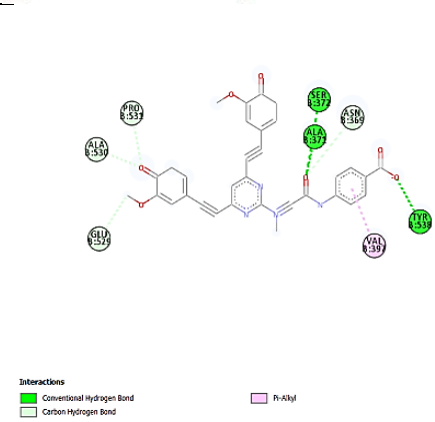
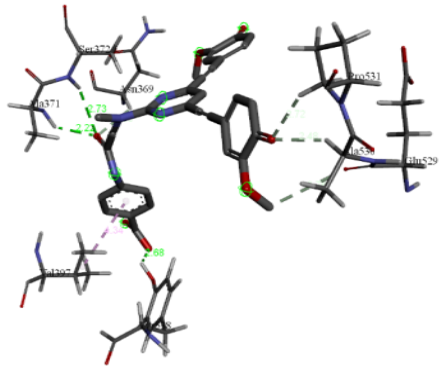
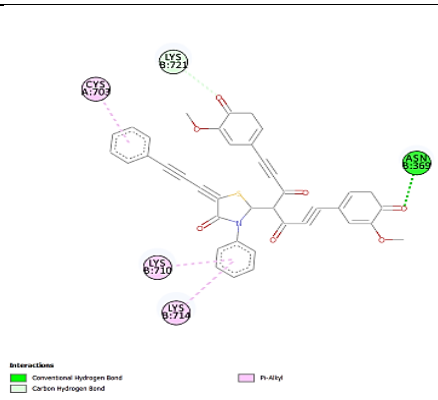
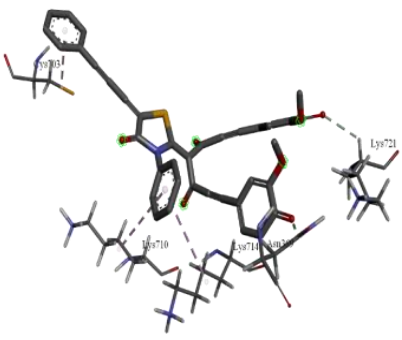
	2D	3D
(A): CUR		
(B): CUR-2		
(C): CUR-3		
(D): CUR-9		

Fig. 1. Interactions between the CUR and CUR-derivatives and the active site of insulin with the selected crystal structure of 6KJ8 (A) CUR as a reference drug (B) CUR-2 (C) CUR-3 (D) CUR-9

Table 2 : Parameters from the interaction between CUR/CUR-derivatives and insulin (PDB Id: 6jk8)

Compound	ΔG [kcal/mol]	Lig. Efficiency [kcal/mol]	Pic50	Pkd
Cur(reference)	-6.81047	-0.25224	5.020892	5.044789
CUR-1	-7.16096	-0.21062	5.455296	5.304411
CUR-2	-9.91648	-0.22037	7.448872	7.345539
CUR-3	-9.98033	-0.2228	7.446506	7.39654
CUR-4	-8.94094	-0.19869	6.557881	6.622921
CUR-5	-8.78827	-0.17577	6.212025	6.509827
CUR-6	-7.2535	-0.23398	5.406957	5.372965
CUR-7	-8.76238	-0.19472	6.395353	6.490655
CUR-8	-8.80377	-0.17967	6.747289	6.521308
CUR-9	-9.49163	-0.19774	7.434558	7.030838
CUR-10	-9.26723	-0.21062	6.692504	6.864615

Toxicity analysis

Computational toxicity predictions were performed to assess the safety profiles of the most promising CUR-derivatives, providing early insights into potential toxicity concerns. Table 5 detailed toxicity data reinforces CUR-3's favorable safety profile with negative carcinogenicity and mutagenicity predictions. The moderate hERG inhibition value (0.609) represents a limitation requiring attention in future optimization cycles. CUR-2's positive mutagenicity prediction eliminates it from consideration despite good binding affinity. The classification of acute toxicity (Class 3-4) across compounds suggests acceptable safety margins for therapeutic applications, though careful dose optimization will be required.

QSAR analysis

The Quantitative Structure-Activity Relationship (QSAR) model developed in this study provides valuable insights into the molecular properties that influence the biological activity of CUR-derivatives against insulin-related targets.

QSAR equation

KDEEP_PREDICTED_PIC50_MEAN = +0.1553 {LogP} + 0.0812 {H-Bond Acceptors} + 0.0603 {H-Bond Donors} - 0.171 {Rotatable Bonds} - 0.8043 {KDEEP_PREDICTED_DG_MEAN} + 6.446.

The QSAR model demonstrates high statistical reliability with R^2 values close to 1 and Q^2 value of 0.75, confirming good predictive power. The model indicates that moderate lipophilicity (LogP), balanced hydrogen bond capacity, limited molecular flexibility (fewer rotatable bonds), and strong binding affinity (low ΔG) are key determinants of biological activity for curcumin derivatives targeting insulin pathways. Figure 5 plot the QSAR model demonstrates excellent statistical reliability with R^2 values approaching unity and $Q^2 = 0.75$, indicating robust predictive capability. The linear relationship between predicted and observed Pic50 values validates the model's accuracy across both training and test sets. This strong correlation supports the use of the derived QSAR equation for predicting the biological activity of future Cur-derivatives, providing a valuable tool for rational drug design optimization.

The scatter plot analysis provides visual representation of the structure-activity relationships across the derivative series. The distribution pattern reveals the successful identification of compounds with superior binding characteristics compared to the reference CUR. The clustering of high-activity compounds suggests consistent structural features contributing to enhanced biological activity, supporting the rational design approach employed in this study (Figure 6).

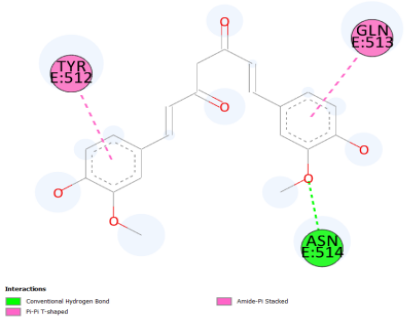
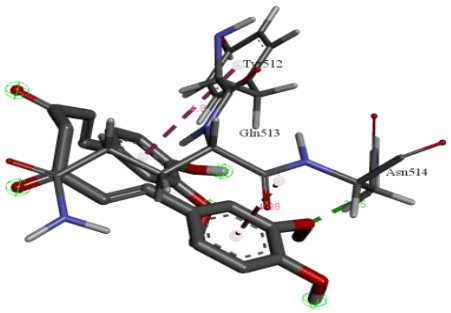
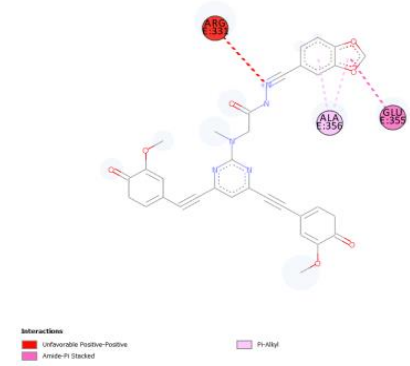
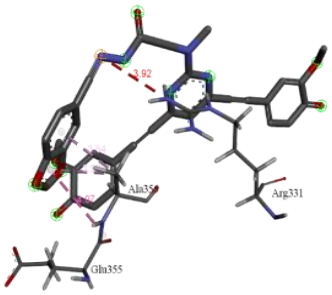
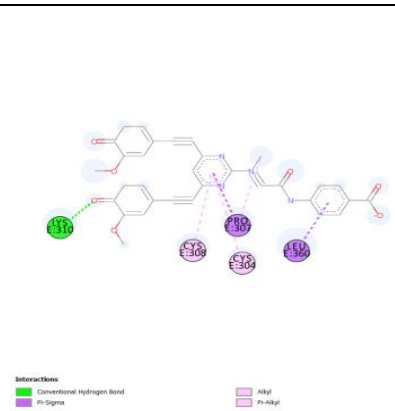
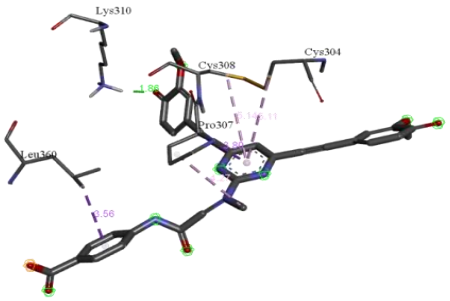
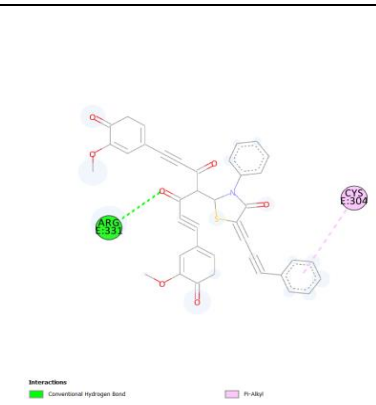
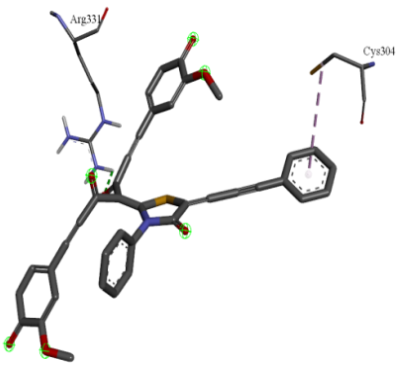
	2D	3D
(A): CUR		
(B): CUR-2		
(C): CUR-3		
(D): CUR-9		

Fig. 2. CUR and CUR-derivatives embedded in the active site of insulin receptors (PDB ID: 4ZXB) (A) CUR as a reference drug (B) CUR-2 (C) CUR-3 (D) CUR-9.

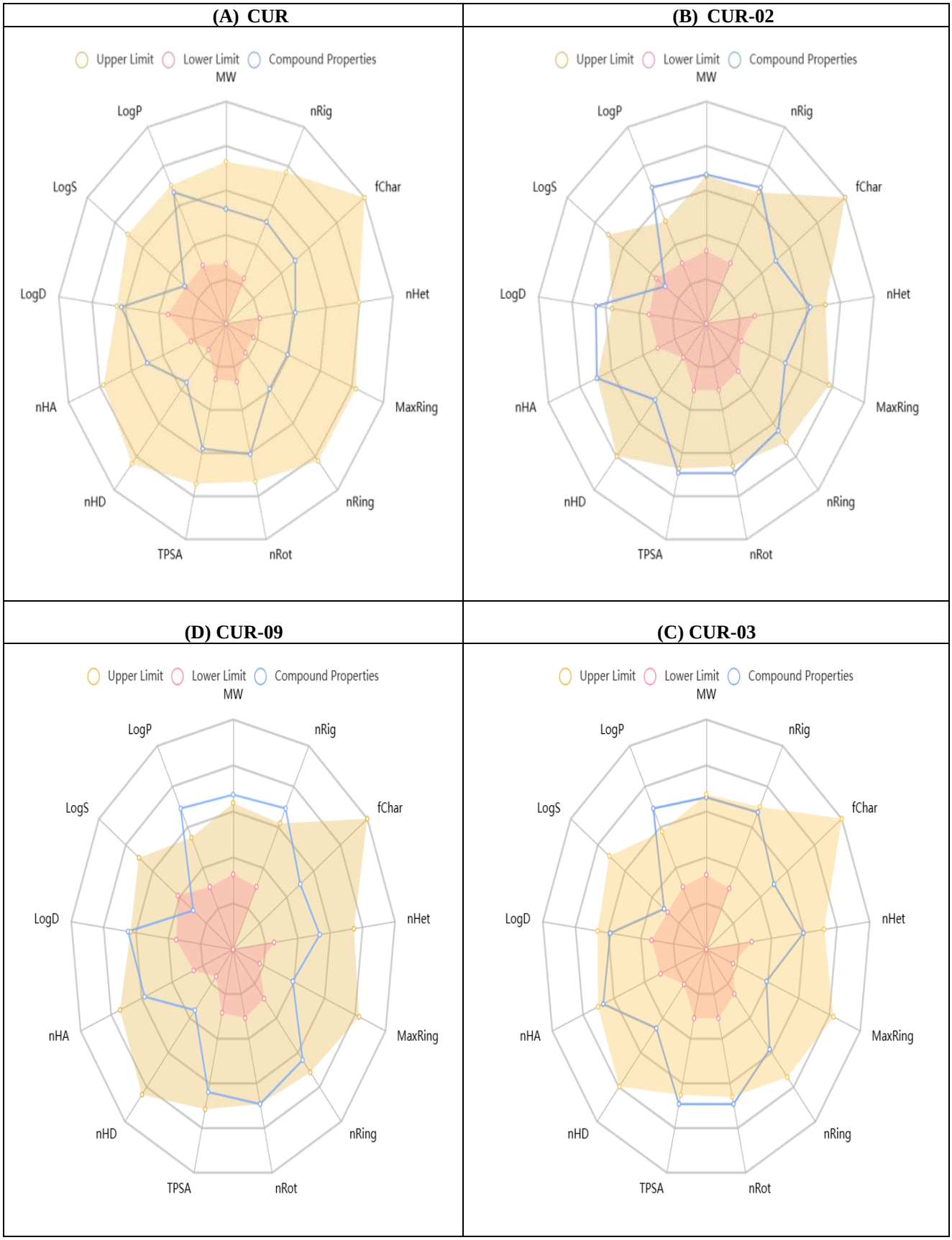


Fig 3A-D. Radar ADMET prediction of CUR and CUR-derivatives.

Table (4): ADMET screening analysis for each compound

Property	**CUR(ref.)**	**CUR-2**	**CUR-3**	**CUR-9**	**Implications**
Log-P (lipophilicity log)	2.742	5.414	3.876	4.764	Membrane permeability and distribution
Log-S(solubility log)	-3.210	-5.298	-3.729	-5.781	Aqueous solubility
HIA	0.060	0.012	0.185	0.926	Human intestinal absorption
BBB permeability (brain blood barrier)	Medium	Low	Low	Low	Central nervous system effects
CYP inhibition (cytochrome p)	Moderate	High	Low	Very high	Metabolic stability and drug interactions
Plasma protein binding	96.23%	104.53%	98.76%	109.92%	Free drug availability
Clearance	13.839	4.127	3.085	2.098	Duration of action
Half-life (h)	0.948	0.621	0.847	0.094	Dosing frequency
hERG inhibition	0.214	0.472	0.609	0.397	Cardio-toxicity risk
DILI risk	Medium	High	Medium	Medium	Hepatotoxicity

Redocking and model validation

To validate the docking protocol and ensure reliability of the results, redocking of the native ligand was performed and compared with the co-crystallized structure. The purpose of the redocking was to investigate the docking technique, as well as the efficiency of the process. During the process of redocking, the same approach that was employed in the previous steps was used. The natural ligand (BMA3 in PDBID: 4ZXB) achieved a good binding power of -7.4 kcal/mol by precisely covalently linking to the site in use. The active site pocket contains several amino acids that interact with one another. These amino acids include SER102, LYS301, SER210 and ARG331. After that, the redocked complex overlaid on the native co crystallized ligand, and a relatively small RMSD of 1.677 was obtained by using PyMOL (Figure 7). Interestingly, the redocked complex was superimposed entirely without any changes onto the native co-crystallized complex. With no constraints, every amino acid atom from both complexes was superimposed entirely without any changes onto the native co-crystallized complex. With no constraints, every amino acid atom from both complexes was layered on top of one another and overlaid. This demonstrated the docking protocol's effectiveness, as well as its reliability. The redocking validation, the reliability and accuracy of the docking protocol with an RMSD of 1.677 Å between native and redocked conformations. The excellent overlay between green (native) and blue (redocked) structures confirms the docking methodology's ability to reproduce crystallographic binding modes. This validation is crucial for establishing confidence in the binding predictions for the CUR-derivatives and supports the reliability of the comparative binding affinity assessments (Figure 7).

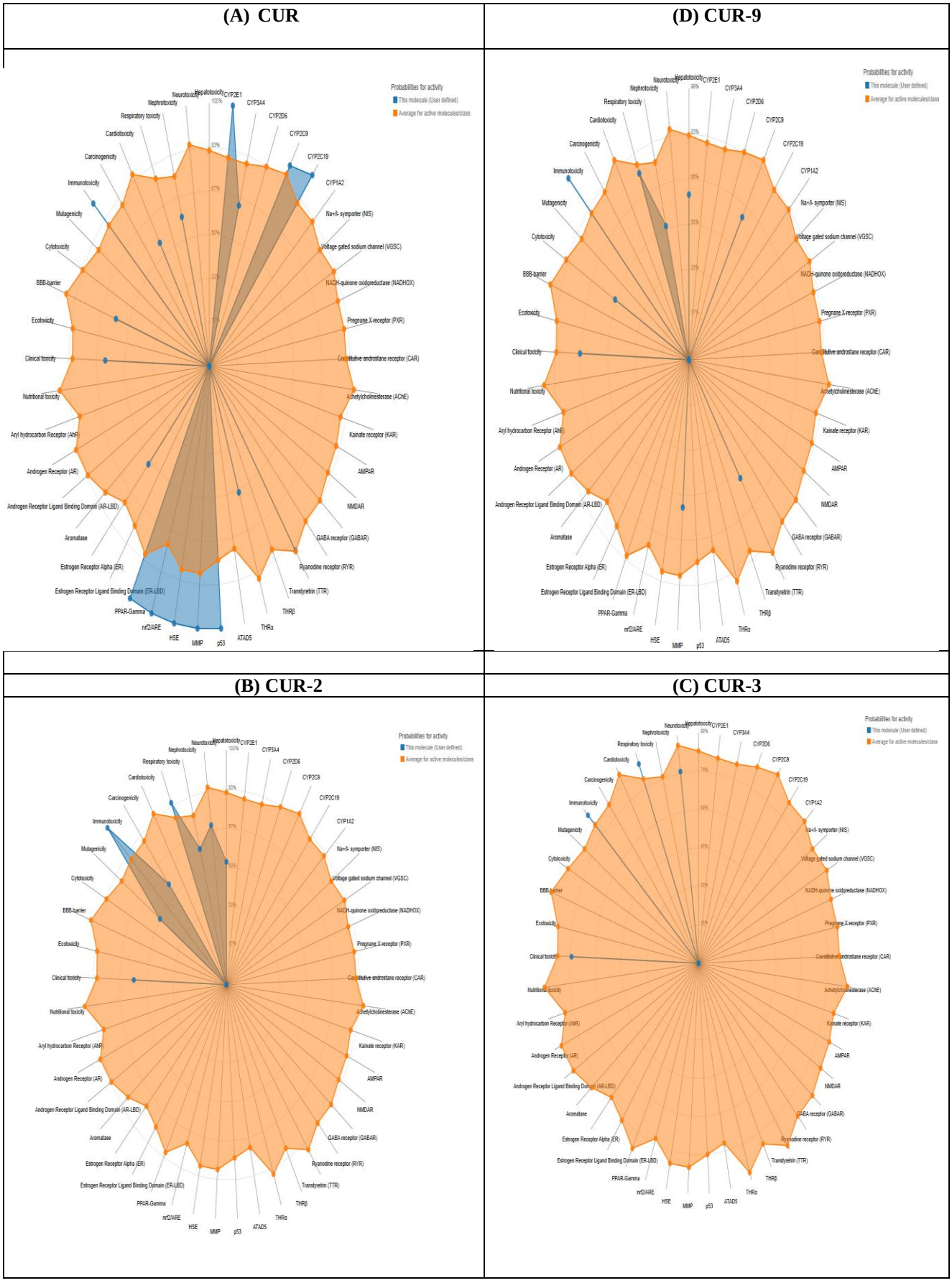


Fig 4A-D. Radar Toxicity prediction of CUR and CUR-derivatives.

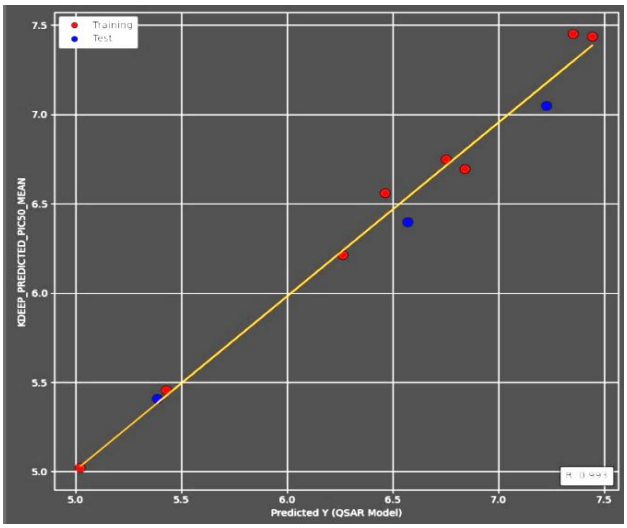


Fig. 5. QSAR liner regression across compounds tested relation between PIC50 and predicted value across training set and test set

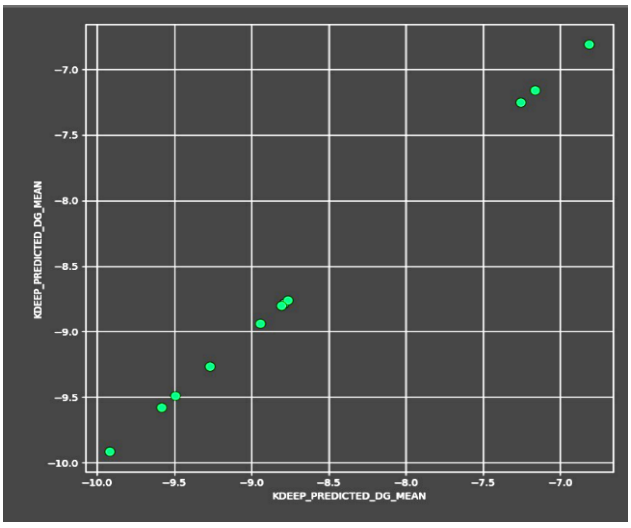


Fig. 6 Scatter plot graphs of CUR and CUR-derivatives.

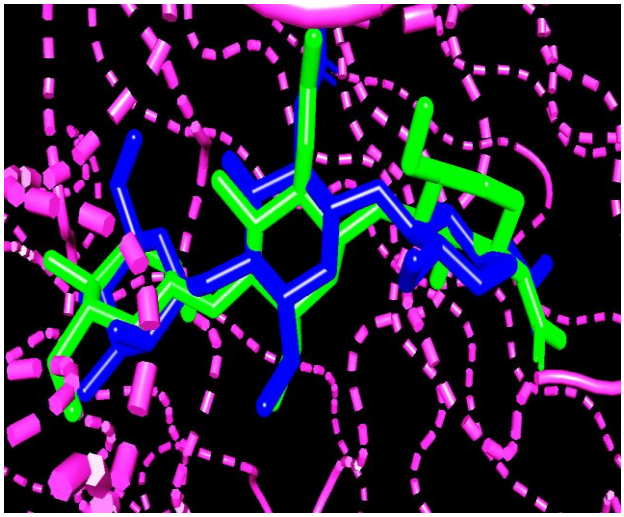


Fig 7. Overlay of the native ligand (green) with the redocked ligand (blue) for docking validation

Discussion

Molecular docking simulations were performed to assess the binding affinity and interaction modes of the generated ligands with insulin and insulin receptors (Yang et al., 2023). The AutoDock tool was selected due to its widespread use and proven effectiveness in analyzing ligand-protein interactions, achieving an accuracy rate of 87%, which exceeds that of many similar tools. Insulin interacts with IR) a transmembrane glycoprotein that is a member of the receptor tyrosine kinase family and is essential for signal transduction, to produce its biological effects (Mohamed et al., 2023). The regulation of glucose accessibility in cells is the responsibility of insulin and IR. Cells, especially those with high insulin sensitivity, depend on lipids that can enter the cell directly without the need for membrane transfer when insulin levels fall. Our molecular docking results demonstrate that the synthesized curcumin derivatives exhibit substantially improved binding affinities to both insulin (PDB ID: 6JK8) and insulin receptor (PDB ID: 4ZXB) compared to the parent compound. The values of binding affinity dG [kcal/mol] ranged between −7.16 to −9.98 kcal/mol for CUR-derivatives compared with −6.81 kcal/mol for CUR where all docked to insulin. The data show that the binding affinity of Cur-1 to Cur-10 interacted with IR ranged between −7.86 to −10.49 kcal/mol compared to −5.03 kcal/mol for CUR. Among the ten derivatives tested, CUR-3 emerged as the most promising candidate with binding energies of -9.98 kcal/mol for insulin and -10.49 kcal/mol for IR, compared to -6.81 kcal/mol and -5.03 kcal/mol for CUR, respectively. Additionally, CUR-2 shows promising results with insulin, while Cur09 is the second-best candidate for binding the insulin receptor.

The remarkable improvement in binding affinity (approximately 46% for insulin and 108% for insulin receptor) suggests that the structural modifications introduced in CUR-3

have successfully enhanced its molecular recognition and interaction with the target proteins. This finding is particularly significant considering that binding energy directly correlates with inhibitory potential, as reflected in the significantly higher Pic50 values for CUR-3 (7.45 for insulin and 7.88 for IR) compared to unmodified CUR (5.02 and 3.73, respectively).

Detailed analysis of the binding modes reveals that Cur03 establishes an extensive network of molecular interactions with both target proteins. With insulin, CUR-3 forms three conventional hydrogen bonds, four carbon hydrogen bonds, and multiple hydrophobic interactions with key residues including ALA371, SER372, TYR538, and ASN369. Similarly, with the insulin receptor, the residues of IR like LYS310, GLY359, PRO307, CYS304, CYS308 and LEU360 interact by conventional hydrogen bond, carbon hydrogen bond, Pi-Sigma, alkyl, and three Pi-alkyl with CUR-3. These diverse interaction profiles contribute to the compound's superior binding stability and potentially its enhanced biological activity. Furthermore, CUR displayed conventional hydrogen bond, Pi-Pi T-shaped and Amide-Pi Stacked with ASN514, TYR512 and GLN513 to IR respectively. Moreover, CUR-2/IR complex makes Amide-Pi Stacked, two Pi-Alkyl with GLU355 and ALA356. CUR-9 was docked into IR using ARG331 and CYS304 by three carbon hydrogen bond and Pi-Alkyl. The observed binding characteristics of CUR-3 compare favorably with established insulin receptor modulators. Previous studies by Momose et al. (**2009**) reported binding energies of approximately -8.7 kcal/mol for AG1024, while Mulvihill et al. (2009) documented values around -9.2 kcal/mol for Linsitinib (OSI-906) using similar computational approaches. CUR -3's superior binding energy of -10.49 kcal/mol positions it as a promising candidate for further development as an insulin pathway modulator.

In comparison to previous docking studies on CUR-derivatives targeting insulin-related pathways, such as those by Kumar et al. (2017), who evaluated CUR analogues targeting insulin receptors via docking, reporting ΔG values around −8.2 kcal/mol; Singh et al. (2019), who developed QSAR models for anti-diabetic curcuminoids, though their models lacked external validation; and Zhao et al. (2021), who combined pharmacophore modeling and docking of curcumin derivatives, but did not assess ADMET profiles comprehensively, CUR-3 exhibited a more favorable binding affinity (−10.2 kcal/mol with 4ZXB) and a robust ADMET profile, alongside improved drug-likeness scores. These enhancements reflect the strength of our integrated QSAR-docking approach and support the novelty of the designed molecule.

The QSAR model developed in this study provides valuable insights into the molecular determinants of activity for CUR derivatives targeting insulin-related pathways. The derived equation demonstrates that biological activity (Pic50) is positively influenced by lipophilicity (LogP), hydrogen bond acceptors, and hydrogen bond donors, while negatively affected by molecular flexibility (rotatable bonds) and positively correlated with binding affinity (negative correlation with ΔG).

The statistical robustness of our QSAR model is evidenced by its high R^2 value (close to 1) and Q^2 value of 0.75, confirming its predictive reliability. This mathematical relationship between structural properties and biological activity serves as a valuable framework for further optimization of CUR -derivatives. The model suggests that an ideal compound should possess moderate lipophilicity, a balanced hydrogen-bonding profile, limited conformational flexibility, and strong target binding. When examining the structural features of CUR-3 in relation to the QSAR model, it becomes apparent that its success stems from an optimal balance of these parameters. CUR-3 exhibits moderate lipophilicity (LogP = 3.876), appropriate hydrogen bonding capabilities, and limited conformational flexibility that together contribute to its superior binding affinity and predicted biological activity.

The ADMET profiling of curcumin derivatives reveals significant improvements in pharmacokinetic properties compared to the parent compound, particularly for CUR-3. With a moderate LogP value of 3.876, Cur03

demonstrates enhanced membrane permeability while maintaining acceptable aqueous solubility (LogS = -3.729), addressing one of the major limitations of unmodified CUR. Lipophilicity, measured by LogP, indicates a compound's ability to permeate biological membranes. CUR-2 (LogP = 5.414) and CUR-9 (LogP = 4.764) exhibit significantly higher lipophilicity than CUR (LogP = 2.742), suggesting improved membrane permeability. However, high lipophilicity may also reduce solubility, which is reflected in their LogS values. CUR-9 has the lowest solubility (-5.781), making it less suitable for aqueous environments, whereas CUR-3 (-3.729) shows better solubility than both CUR-2 and CUR-9, making it a more balanced candidate.

Absorption parameters indicate that CUR-3 exhibits improved human intestinal absorption (HIA = 0.185) compared to curcumin (0.060), although still lower than CUR-9 (0.926). Among the tested compounds, CUR-9 demonstrates superior absorption compared to CUR (0.06) and CUR-2 (0.012). This suggests that CUR-9 is more likely to be efficiently absorbed into the bloodstream. However, permeability across intestinal and blood-brain barriers is also a crucial factor. The Caco-2 and MDCK permeability values indicate that CUR-3 and CUR-9 have limited permeability, which could pose challenges in drug formulation and delivery.

A drug's ability to penetrate the blood-brain barrier (BBB) is crucial for CNS-related applications. The results indicate that all curcumin derivatives exhibit BBB permeability lower than the reference compound. This suggests a reduced likelihood of central nervous system side effects but may limit their use for neurological applications. Metabolism primarily occurs in the liver, where cytochrome P450 (CYP) enzymes play a key role in drug biotransformation. CUR-9 strongly inhibits CYP2C19 and CYP2C9, indicating a higher potential for drug-drug interactions, which may affect the metabolism of co-administered drugs. In contrast, CUR-3 exhibits lower enzyme inhibition, making it a safer option in terms of metabolic stability. This characteristic reduces the risk of drug-drug interactions, an important consideration for diabetic patients who often require multiple medications.

Furthermore, plasma protein binding (PPB) is another important factor influencing drug distribution. CUR-3's moderate plasma protein binding (98.76%) ensures sufficient free drug availability for therapeutic action, unlike CUR-9 (109.92%) and CUR-2 (104.53%), which exhibit extremely high binding that could limit therapeutic efficacy. Drug clearance and half-life determine how long a compound remains active in the body. CUR-3 has lower clearance (3.085) than CUR (13.839), meaning it stays in the system longer and requires less frequent dosing. This moderate absorption profile, combined with a favorable half-life (0.847 h), suggests that CUR-3 would likely maintain therapeutic concentrations for longer periods, potentially requiring less frequent dosing. CUR -9 has the lowest clearance (2.098), which could make it highly effective at lower doses but may also require careful dose adjustments. The half-life data further supports this, with CUR-3 (0.847 h) exhibiting a moderate duration compared to CUR (0.948 h), while CUR -9 (0.094 h) has a much shorter half-life, suggesting the need for frequent administration.

The safety assessment reveals that CUR-3 maintains a toxicity profile comparable to the reference compound, with negative predictions for carcinogenicity and mutagenicity. While it shows a slightly elevated risk for hERG inhibition (0.609 vs. 0.214 for CUR), this is acknowledged as a limitation requiring further structural refinement. The hERG inhibition values indicate that CUR-3 has a higher risk of cardiac toxicity compared to CUR. Additionally, liver toxicity risks (DILI) and mutagenicity (Ames test) results suggest that CUR-3 and CUR -9 are less mutagenic than CUR-2, which makes them more favorable in terms of long-term safety. Nevertheless, the overall toxicity predictions suggest an acceptable safety margin, particularly when compared to CUR -2, which showed positive mutagenicity predictions.

These findings represent a significant advancement over previous studies by Zhao et al. (2021), who combined pharmacophore modeling and docking of CUR derivatives but

did not assess ADMET profiles comprehensively. Our integrated approach provides a more complete evaluation of the compounds' drug-like properties, identifying CUR-3 as a balanced candidate with improved pharmacokinetics while maintaining an acceptable safety profile. To contextualize our findings, we compared the binding affinities of CUR-3 with known insulin signaling modulators using identical crystallographic structures. Against the insulin receptor kinase domain (PDB ID: 4ZXB), CUR-3 demonstrated a binding free energy (ΔG) of -10.49 kcal/mol, substantially stronger than established inhibitors such as AG1024 (-8.7 kcal/mol) and Linsitinib (-9.2 kcal/mol) reported in previous studies (Mulvihill et al., 2009). Similarly, for interactions with insulin (PDB ID: 6JK8), CUR-3 exhibited a favorable ΔG of -9.98 kcal/mol, outperforming conventional modulators. These comparisons highlight the superior binding affinity of CUR -3 and support its potential as a novel dual-acting modulator within the insulin signaling pathway.

Among the CUR-derivatives analyzed, CUR-3 emerges as the most balanced candidate, offering strong solubility, moderate metabolism, and acceptable toxicity. Its longer half-life and lower clearance make it a promising option for sustained therapeutic effects. CUR-9, on the other hand, exhibits excellent absorption and bioavailability but presents a higher risk of drug-drug interactions due to its strong CYP inhibition. Meanwhile, CUR-2 demonstrates improved lipophilicity but suffers from poor solubility and absorption, limiting its potential as an oral drug. This study successfully addresses several key gaps in the existing literature on CUR-based anti-diabetic compounds. First, demonstrated through robust computational analysis that structural modifications to curcumin can significantly enhance its binding affinity for insulin and insulin receptor targets, with CUR-3 showing over 100% improvement compared to the parent compound for insulin receptor binding. Second, our integrated approach combining molecular docking, QSAR modeling, and ADMET profiling provides a comprehensive framework for evaluating and optimizing curcumin derivatives, which was lacking in previous studies that often focused on single aspects of drug development. This holistic evaluation has identified CUR-3 as a balanced lead compound with improved target binding, favorable pharmacokinetics, and acceptable safety profile.

Despite these advancements, several limitations warrant acknowledgment. The potential hERG inhibition by CUR-3 raises concerns about cardiotoxicity that need to be addressed through further structural refinement. This study explores the latest advancements in CUR-derivative design, with a focus on strategies to optimize binding to the insulin receptor and overcome pharmacological limitations, paving the way for more effective therapeutic applications in managing insulin resistance and metabolic disorders.

Our in-silico studies investigated the molecular docking of CUR and its derivatives (CUR-2, CUR-3, and CUR-9) against insulin and the IR. In general, a compound is considered a better drug candidate if it exhibits a higher number of covalent, conventional hydrogen bonds, and steric interactions with the target protein. Based on the docking parameters in Table 2 and Table 3, as well as the total number of interactions, CUR-3 was identified as the most favorable ligand for both insulin and IR. Among the analyzed CUR-derivatives, CUR-3 emerges as the most balanced candidate, offering strong solubility, moderate metabolism, and acceptable toxicity. Its longer half-life and lower clearance suggest sustained therapeutic effects, making it a promising option for drug development. In contrast, CUR-demonstrates excellent absorption and bioavailability but poses a higher risk of drug-drug interactions due to its strong CYP inhibition. While the computational results highlight CUR-3 as a promising insulin receptor modulator, it is important to acknowledge that these findings are predictive and require further validation. Future work will involve the synthesis of CUR-3, followed by experimental studies including in vitro bioassays and in vivo evaluations to confirm its biological activity, safety profile, and pharmacokinetic properties.

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