Computational Investigation of Coumarin-Triazole-Chalcone Hybrids as Potential Antidiabetic Agents: Molecular Docking and ADMET Studies

Mahesh Akki,[1]* Vinuta Kamat,[2] Yallappa Jogammanavar[1]
[1]*Department of First Year Engineering, Smt. Kamala and Sri Venkappa M. Agadi College of Engineering & Technology,*
Lakshmeshwar-582116, Karnataka, India
[2]*Department of Chemistry, Dayananda Sagar College of Engineering,*
Bangalore, 560078, Karnataka, India
*Corresponding author: Dr. Mahesh Akki; Email: mahesh.gs@agadiengcollege.com

Abstract: **The current work focuses on the design and computational assessment of new coumarin-triazole-chalcone hybrids as possible carbohydrate hydrolyzing enzyme inhibitors for diabetic control. To study possible antidiabetic action, a series of derivatives (1a-1j) were designed and tested using molecular docking against α -amylase (PDB: 1B2Y) and α -glucosidase (PDB: 3W37). The docking data showed that the majority of the proposed compounds had substantial binding affinities for both enzymes. Compounds 1a and 1b have the greatest binding affinity to α-amylase (-10.8 kcal/mol) forming stable interactions with critical catalytic residues in the active region. Docking against α-glucosidase showed that compound 1f (-11.4 kcal/mol) had binding energy equivalent to the reference inhibitor acarbose, while compounds 1b and 1j also had substantial interactions with the enzyme. In addition, the ADMET and pharmacokinetic parameters of chosen drugs were predicted using the pkCSM web server. The results showed good drug-likeness, high intestine absorption, acceptable permeability, moderate distribution and a minimal mutagenesis risk. The hybrids were also expected to have poor blood-brain barrier penetration, implying little central nervous system exposure. The computational findings indicate that the coumarin-triazole-chalcone hybrids have good inhibitory ability against α-amylase and α-glucosidase, making them suitable lead candidates for developing novel antidiabetic medicines.**

Keywords: Coumarin; Triazole; Chalcones; Antidiabetic; Molecular docking; Computational evaluation

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic condition characterized by persistent hyperglycemia caused by abnormalities in insulin production, action or both. Diabetes has been increasingly prevalent worldwide in recent decades owing to aging populations, sedentary lifestyles, urbanization and nutritional changes. According to international health assessments, hundreds of millions of people worldwide are afflicted with estimates for a significant increase in the future decades [1]. This growing burden has extensive consequences for public health systems, quality of life and socioeconomic development as diabetes is linked to significant sequelae such as cardiovascular disease, nephropathy, neuropathy and retinopathy. Long-term glycaemic management remains a significant issue, despite the availability of many antidiabetic medication classes [2]. Existing medications are sometimes restricted by unpleasant effects, subsequent failure, threat of hypoglycaemia, weight gain and high cost particularly in low- and middle-income countries. Current therapies focus on managing hyperglycemia rather than offering a cure or avoiding long term consequences. These limitations underscore the importance of developing innovative treatment techniques and biological targets for diabetes control that is safer and more effective [3, 4].

Inhibiting major carbohydrate-digesting enzymes in the gastrointestinal tract is a potential technique for managing type 2 diabetes specifically postprandial hyperglycemia. α-amylase hydrolyzes complicated starches into oligosaccharides, whereas α-glucosidase converts oligosaccharides and disaccharides into absorbable monosaccharides like glucose [5, 6]. Excessive or fast activity of these enzymes causes acute postprandial blood glucose increases which are directly connected to the development of insulin resistance and cardiovascular problems. Selective inhibition of α-amylase and α-glucosidase is a proven therapeutic technique for reducing postprandial hyperglycemia [7]. Currently available α-glucosidase and α-amylase inhibitors such as acarbose, miglitol and voglibose have clinical utility, but are frequently associated with gastrointestinal side effects including flatulence, abdominal discomfort, and diarrhoea due to fermentation of unabsorbed carbohydrates in the colon. These tolerability difficulties might jeopardize patient compliance and hinder widespread use. New α-amylase and α-glucosidase inhibitors with enhanced effectiveness, selectivity, and safety are critically required [8].

Medicinal chemistry plays a pivotal role in the discovery and optimization of such novel antidiabetic agents. By investigating various chemical scaffolds and SAR, it is feasible to create compounds that control these enzyme targets while reducing side effects [8, 9]. Coumarins are benzopyrone derivatives made up of a fused benzene ring and α-pyrone ring. They are a compact scaffold that may be fine-tuned for electronic and lipophilic characteristics by various substitutions. This structural flexibility supports being recognized as a privileged scaffold in medicinal chemistry and has enabled the construction of various hybrids with other heterocycles to boost potency and selectivity [10, 11]. Coumarin derivatives exhibit multitarget antidiabetic properties. Coumarins, both natural and synthetic derivatives can improve glycemic control and prevent complications like nephropathy and cardiomyopathy by inhibiting intestinal α-glucosidase, decreasing glucose absorption, increasing insulin secretion or sensitivity, activating AMPK, modulating PTP1B and GSK-3β, inhibiting SGLT1/2, and reducing oxidative

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stress and AGE formation [12-14]. Litrature has demonstrated that Coumarin-triazole and coumarin-chalcone hybrids further increase α-amylase inhibition and insulin resistance, validating the coumarin core as a reasonable design feature for novel antidiabetic drugs [15, 16].

Triazoles are five membered aromatic heterocycles with three nitrogen atoms. They form a planar, highly hydrogen-bonded and metabolically stable ring that acts as a bio isostere for amide or ester groups and a strong linker to other pharmacophores [17, 18]. Their ability to engage in π–π, hydrogen-bond and coordination interactions with enzyme active-site residues supports tight binding and high selectivity. Numerous 1,2,3-triazole-based α-glucosidase inhibitors have been improved by SAR and docking surpassing reference medicines in potency [19, 20].

Chalcones have a 1,3-diphenyl-2-propen-1-one core with an α,β-unsaturated carbonyl system and two aromatic rings that can be easily tuned [21]. SAR studies indicate that hydroxyl, prenyl, and geranyl substituents, particularly certain hydroxy patterns on both aryl rings, significantly enhance inhibition of α-amylase and α-glucosidase, among other antidiabetic targets [22, 23]. Driven by the medicinal significance of coumarins, triazoles and chalcones we intended to conjugated these pharmacologically important scaffolds into a single framework and evaluate them for antidiabetic activity using computational approaches.

II. Results and Discussion

A. Design strategy

The coumarin-triazole-chalcone hybrids were developed based on the pharmacological significance of the individual scaffolds and their documented biological activities. The coumarin moiety was chosen as the core scaffold and it was attached to the chalcone unit using a 1,2,3-triazole linker. The triazole ring acts as a stiff and metabolically stable bridge allowing for efficient contact with the target enzyme's active site residues. Furthermore, structural modifications were introduced on the aromatic ring of the chalcone moiety by introducing various electron-donating and electron-drawing substituents in order to examine their effect on binding affinity and electronic characteristics (Figure 1).

B. Molecular docking studies

The molecular docking studies were carried out for the designed hybrids against α-amylase (PDB: 1B2Y) and α-glucosidase (PDB: 3W37) proteins to evaluate their binding affinity and interaction patterns within the active sites of these proteins. The structure of human pancreatic alpha-amylase in complex with the carbohydrate inhibitor acarbose (PDB: 1B2Y) [24] and sugar beet alpha-glucosidase with acarbose (PDB: 3W37) [25] was downloaded from the protein database (www.rcsb.org) Before protein preparation, the inhibitors, other ligands, and water molecules were deleted from the protein to obtain clean protein. Polar hydrogen atoms and Kollman charges were added to the protein before docking [26]. The protein (PDB ID: 1B2Y) grid box's centre was set to 62, 56 and 54 while the number of points in the x, y, and z dimensions was set to 19.580, 7.937 and 48.902 Å, respectively. The protein (PDB ID: 3W37) grid box's centre was set to 70, 64 and 92 while the number of points in the x, y, and z dimensions was set to 23.144, -24.547 and -51.548 Å, respectively. The chemdraw tool was used to determine the 2D orientations of the synthesised molecules, which were then

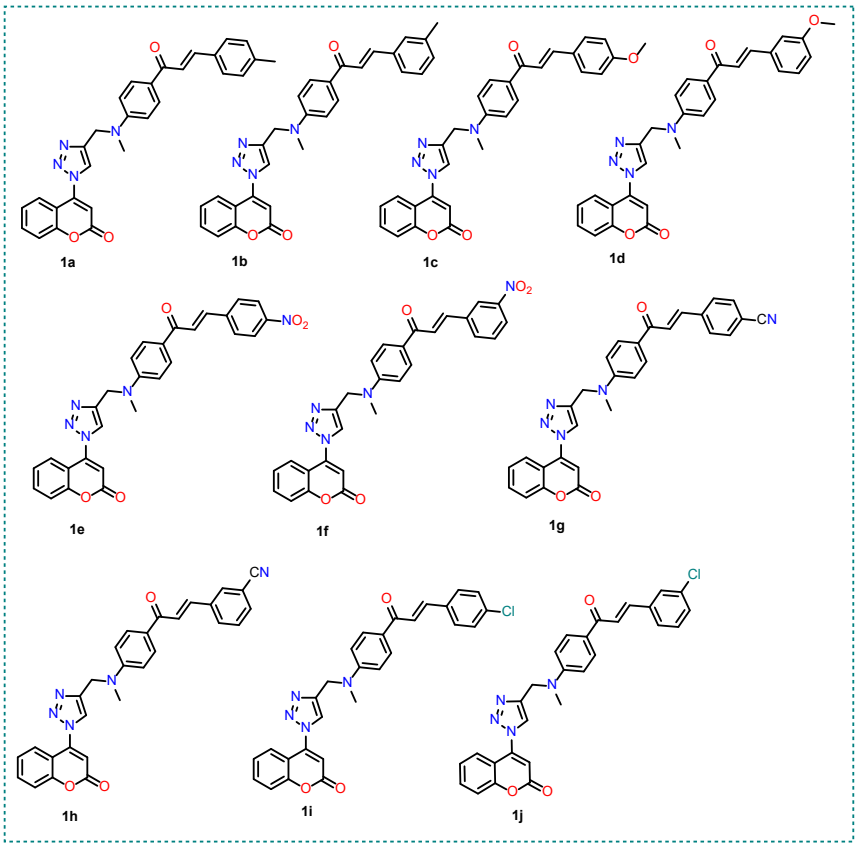

Fig. 1. Designed coumarin–triazole–chalcone hybrid compounds.

converted into the most energy-efficient 3D structures via a minimization method. Furthermore, the claims made by Gasteiger Rotatable bonds and nonpolar hydrogen atoms were constructed using AutoDock 4.2. When docking each compound with Auto Dock Vina. The docking result as displayed by Discovery Studio software [27].

1) α-Amylase

α-Amylase breaks down complex carbs like starch and glycogen into oligosaccharides and maltose during digestion. This enzyme is predominantly produced by the pancreas and salivary glands and plays an important function in regulating glucose availability in the body. Excessive α-amylase activity causes fast breakdown of carbohydrates, leading to an abrupt spike in blood glucose levels. This is a serious problem in type 2 diabetes. Inhibiting α-amylase can effectively manage postprandial hyperglycemia by reducing carbohydrate digestion and glucose absorption. Several antidiabetic medications, including acarbose work on this mechanism.

TABLE I. DOCKING RESULTS OF THE SYNTHESIZED DERIVATIVES AGAINST A-AMYLASE (PDB: 1B2Y)

Compound code	Binding affinity (kcal/mol)
1a	-10.8
1b	-10.8
1c	-10.5
1d	-10.4
1e	-10.4
1f	-10.7
1g	-10.7
1h	-9.9
1i	-10.6
1j	-10.7
acarbose	-16.4

The docking data showed that all designed compounds had substantial binding affinities ranging from -9.9 to -10.8 kcal/mol, indicating favourable interactions with the catalytic pocket of α-amylase. Among the studied derivatives, hybrids **1a** and **1b** had the greatest binding affinity (-10.8 kcal/mol), followed by **1f**, **1g**, and **1j** (-10.7 kcal/mol), while **1i** and **1c** had binding energies of -10.6 and -10.5 kcal/mol (**Table 1**). The affinities for **1d** and **1e** were somewhat lower (-10.4 kcal/mol), whereas 1h had the lowest binding energy (-9.9 kcal/mol) in the synthesized series. For comparison, the standard inhibitor acarbose exhibited a binding affinity of -16.4 kcal/mol which is expected due to its highly polar structure capable of forming multiple hydrogen-bond interactions with the enzyme. The docking poses show that the derivatives engage with critical amino acid residues in the active site of α-amylase by a variety of interactions, including typical hydrogen bonding, carbon-hydrogen bonding, π-π stacking, π-σ, π-cation and π-alkyl. TYR62, TRP59, HIS201, LYS200, GLU233, ASP197, ASP300, LEU162 and GLN63 are common residues that help to stabilize the ligand-protein complex. The synthesized scaffolds' aromatic rings promote π-π stacking interactions with Tyr62 and Trp59, whereas polar functional groups like carbonyl and heterocyclic nitrogen atoms contribute to hydrogen bonding with LYS200, GLN63, and GLU233. Additionally, π–cation and π–anion interactions involving HIS201 and GLU233 further stabilize the ligand within the catalytic pocket. The binding interactions of compound **1a** at the active site of the protein α-amylase is depicted in **Figure 2**.

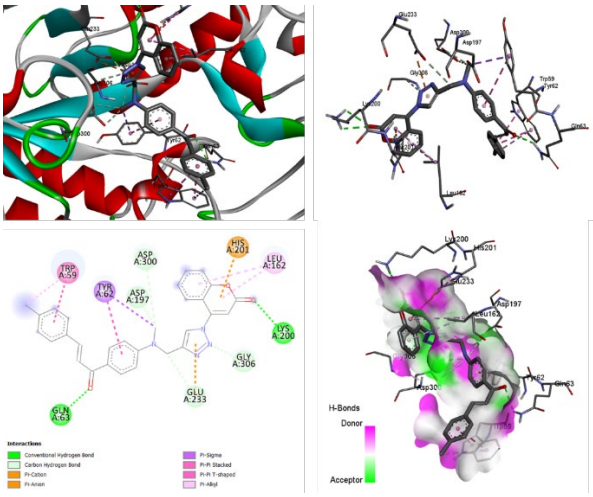

Fig. 2. Binding interactions of compound 1a at the active site of the protein α-amylase (PDB: 1B2Y).

The docking results indicate that the coumain-triazole-chalcone hybrids fit well into the binding cavity of α-amylase, forming several stabilizing contacts with catalytically essential residues. Compounds **1a**, **1b**, **1f**, **1g** and **1j** have substantial binding energies, indicating their potential as α-amylase inhibitors. This might lead to reduced postprandial blood glucose levels by inhibiting carbohydrate hydrolysis. Although the binding affinity is lower than that of the reference drug acarbose, the hybrids show significant interaction capability and a favourable binding orientation, implying that these scaffolds could be used as lead molecules in the development of new antidiabetic drugs.

2) α-Glucosidase

The brush border of the small intestine contains α-glucosidase, an essential enzyme that hydrolyzes carbohydrates. By transforming oligosaccharides and disaccharides into absorbable glucose molecules, it catalyzes the last stage of carbohydrate digestion. The control of postprandial blood glucose levels is largely dependent on this enzymatic mechanism. Rapid α-glucosidase activity increases glucose absorption in those with type 2 diabetes mellitus raising blood sugar levels after meals. As a result, α-glucosidase inhibition is thought to be a successful treatment strategy for managing postprandial hyperglycemia.

TABLE II. DOCKING RESULTS OF THE SYNTHESIZED DERIVATIVES AGAINST A-GLUCOSIDASE (PDB: 3W37)

Compound Code	Binding Affinity (kcal/mol)
1a	-10.9
1b	-11.2
1c	-10.1
1d	-10.6
1e	-10.3
1f	-11.4
1g	-9.7
1h	-8.3
1i	-10.4
1j	-11.0
acarbose	-11.4

The docking findings indicated that the proposed compounds had binding affinities ranging from -8.3 to -11.4 kcal/mol indicating a strong interaction with the enzyme's

active region. Among the tested derivatives the compound **1f** had the greatest binding affinity (-11.4 kcal/mol) that was equivalent to the conventional inhibitor acarbose. This was followed by **1b** (-11.2 kcal/mol) and **1j** (-11.0 kcal/mol) indicating significant interactions with the enzyme's catalytic residues. Compounds **1a** (-10.9 kcal/mol), **1d** (-10.6 kcal/mol), **1i** (-10.4 kcal/mol), and **1e** (-10.3 kcal/mol) likewise had high binding energies (**Table 2**). The docking poses reveal several stabilizing contacts between the proposed ligands and the α-glucosidase binding pocket. Several amino acid residues, including SER497, SER505, LYS506, ARG670, ASP232, GLU301, HIS626, TRP329, PHE476 and ILE233 contribute to ligand stabilization via hydrogen bonds, carbon-hydrogen bonding, π-π stacking, π-anion, π-sigma and π-alkyl interactions. Carbonyl and heterocyclic nitrogen atoms in some compounds act as hydrogen bond donors or acceptors forming strong interactions with residues like SER497, SER505 and LYS506. while aromatic rings in the designed scaffolds promote π-π stacking with residues like TRP329 and PHE476 enhancing binding stability. Electrostatic interactions including π-anion interactions with ASP and GLU residues help stabilize the ligand-protein complex in the catalytic region. The binding interactions of compound **1a** at the active site of the protein α-glucosidase is shown in **Figure 3.**

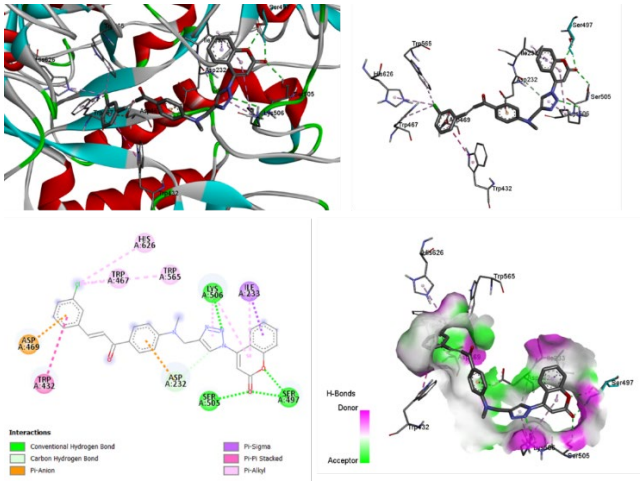

Fig. 3. Binding interactions of compound 1a at the active site of the protein α-glucosidase (PDB: 3W37).

The docking results show that the majority of the developed compounds had binding affinities similar to or somewhat lower than the reference inhibitor acarbose indicating their potential as α-glucosidase inhibitors. The compounds **1f**, **1b**, and **1j** exhibited substantial binding energies and good interactions with critical catalytic residues indicating their potential to decrease α-glucosidase activity and lower postprandial glucose levels. The developed scaffold shows promise for developing novel antidiabetic drugs that target α-glucosidase.

C. ADMET studies

The well recognized Lipinski's Rule of Five [28] and Veber Rule guidelines [29] were used to analyze the ADMET-related physicochemical properties of the designed compounds (**1a–1j**) in order to determine their drug-likeness and oral bioavailability. The results were deduced using Swiss ADME webserver [30]. The majority of hybrids have molecular weights (MW) that are within or very near the suggested limit of ≤500 Da. While compounds **1e** and **1f** marginally surpass the limit (507.5 Da), suggesting a tiny departure but still within a reasonable range for drug-like molecules, compounds **1a–1d**, **1g**, **1h**, **1i**, and **1j** fall within the acceptable range (**Table 3**).

The lipophilicity values (iLogP) of the designed compounds vary from 3.57 to 4.26, which are within the acceptable range (≤5), indicating a balanced hydrophilic-lipophilic nature advantageous for membrane permeability and absorption. The projected water solubility (Log S) values range from -6.68 to -6.07, indicating moderate to poor solubility, which is typical of lipophilic heterocyclic compounds but may nevertheless allow sufficient bioavailability.

Hydrogen bond acceptor (HBA) values range from 5 to 7, whereas hydrogen bond donor (HBD) values are zero for all hybrids, meeting the Lipinski requirements (HBA ≤ 10 and HBD < 5). This shows that the produced compounds have enough hydrogen bonding capability, allowing for beneficial interactions with biological targets. The number of rotatable bonds (nRB) varies from 7 to 8, falling below the Veber rule limit of ≤10, suggesting sufficient molecular flexibility for receptor binding.

Furthermore, the topological polar surface area (TPSA) values range from 81.23 to 127.05 Å², which is under the required threshold of ≤140 Å², indicating adequate oral bioavailability and intestinal absorption. Overall, the ADMET analysis shows that the majority of the designed compounds follow both Lipinski and Veber rules with few exceptions, implying that these molecules have favourable physicochemical properties and may be promising candidates for future pharmacological studies.

TABLE III. PHYSICOCHEMICAL DESCRIPTORS OF THE SYNTHESIZED COMPOUNDS.

Compound	MW	iLog P	Log S	HBA	HBD	nRB	TPSA
Lipinski	≤500	≤5	-	≤10	≤5	-	-
Veber	-	-	-	-	-	≤10	≤140
1a	476.53	4.22	-6.28	5	0	7	81.23
1b	476.53	3.97	-6.28	5	0	7	81.23
1c	492.53	4.17	-6.07	6	0	8	90.46
1d	492.53	4.14	-6.07	6	0	8	90.46
1e	507.5	3.57	-6.68	7	0	8	127.05
1f	507.5	3.61	-6.68	7	0	8	127.05
1g	487.51	3.65	-6.1	6	0	7	105.02
1h	487.51	3.7	-6.1	6	0	7	105.02
1i	496.94	4.01	-6.55	5	0	7	81.23
1j	496.94	4.26	-6.55	5	0	7	81.23

The in-silico pharmacokinetic and toxicity characteristics (ADMET) of the selected compounds **1a**, **1b** and **1j** were predicted using the pkCSM web server and compared to the reference drug Acarbose (**Table 4**). The radar plots (**Figure 4 a-c**) depict the bioavailability radar and six critical physicochemical parameters lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), flexibility (FLEX) and saturation (INSATU). The graphs show that the proposed compounds are mostly inside the optimum range, indicating good drug-likeness and oral bioavailability characteristics. In terms of absorption, the anticipated water solubility values for compounds **1a**, **1b** and **1j** ranged from -6.16 to -6.12, showing intermediate solubility relative to the reference medication. The Caco-2 permeability values (0.47-0.57) indicate adequate membrane permeability although intestinal absorption was projected to be 100% for all three drugs showing good oral absorption. Furthermore, the substances were anticipated to be P-glycoprotein (P-gp) substrates and inhibitors, potentially influencing drug transport and efflux processes.

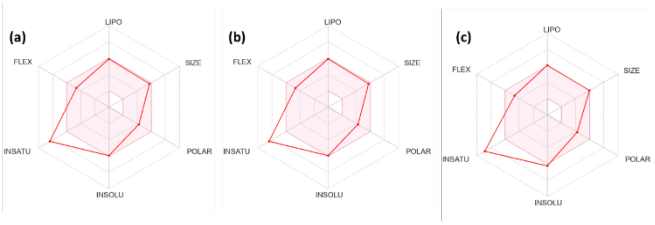

Fig. 4. Radar plots of compound (a) 1a, (b) 1b and (c) 1j

The projected volume of distribution (VDss) values (0.328-0.36) indicates a modest dispersion of the compounds within bodily tissues. The fraction unbound (Fu) values (0.234-0.251) suggest that a moderate part of the chemicals are free in plasma and can exert pharmacological activity. The blood-brain barrier (BBB) permeability values (-0.884 to -1.043) and central nervous system (CNS) permeability values (-1.822 to -1.778) indicate low penetration into the brain, which may minimize the risk of CNS-related adverse effects. In terms of metabolism the proposed compounds were expected to be neither CYP2D6 substrates nor CYP1A2 inhibitors indicating a decreased chance of metabolic drug-drug interactions involving these enzymes. For excretion, the estimated total clearance values (0.72-0.726) reflect modest elimination rates and none of the compounds were anticipated to act as renal OCT2 substrates, suggesting that renal transporter-mediated interactions are improbable. The toxicity evaluation found that all compounds were anticipated to be non-mutagenic using the AMES test and non-sensitizing to skin indicating a positive safety profile. However, the drugs demonstrated expected hepatotoxicity which may need more experimental confirmation.

Abbreviations and cut-off values: Caco2: Cancer coli-2; >0.9 log cm/s, VDss: Volume of Distribution at Steady State; log VDss< -0.15 (low); log VDss> 0.45 (high), BBB: Blood-brain barrier; logBB> 0.3(easily cross BBB); log BB < -1 (poor distribution), CNS: central nervous system logPS> -2 (penetrate CNS); logPS< -3 (unable to penetrate CNS), CYP: Cytochromes-P450, OCT2: Organic Cation Transporter, . The in-silico ADMET prediction was performed using the pkCSM web server

Overall, the ADMET analysis suggests that the designed compounds 1a, 1b and 1j have favourable pharmacokinetic properties, good oral absorption, acceptable metabolic stability and low mutagenic risk indicating that they are promising lead molecules for further development as antidiabetic agents.

TABLE IV. IN-SILICO PREDICTED PHARMACOKINETIC PARAMETERS (ADMET)

Parameters		1a	1b	1j	Standard
Absorption	Water solubility	-6.166	-6.129	-6.128	-1.361
	Caco-2	0.57	0.519	0.47	-0.717
	Intestinal absorption	100	100	100	0
	P-gp substrate	Yes	Yes	Yes	Yes
	P-gp inhibitor	Yes	Yes	Yes	No
Distribution	VDss	0.328	0.352	0.36	-0.833
	Fu	0.251	0.239	0.234	0.569
	BBB	-0.884	-0.868	-1.043	-1.841
	CNS	-1.822	-1.818	-1.778	-6.183
Metabolism	CYP2D6 Substrate	No	No	No	No
	CYP1A2 Inhibitor	No	No	No	No
Excretion	Total clearance	0.72	0.726	-0.05	0.619
	Renal OCT2 substrate	No	No	No	No
Toxicity	AMES toxicity	No	No	No	No
	Hepatotoxicity	Yes	Yes	Yes	No
	Skin sensitization	No	No	No	No

III. CONCLUSION

A series of new coumarin-triazole-chalcone hybrids (1a-1j) were developed and computationally assessed for potential antidiabetic action using molecular docking and in-silico pharmacokinetic experiments. The docking research revealed that some of the hybrids had high binding affinities with both α-amylase and α-glucosidase, indicating that they might limit carbohydrate digestion and lower postprandial glucose levels. Compounds 1a, 1b, 1f, and 1j had the highest binding affinities and interaction characteristics of the series, indicating that they are excellent candidates for future research. The projected ADMET parameters of the chosen compounds demonstrated adequate oral absorption, acceptable permeability, moderate distribution, and minimal mutagenesis risk, confirming their drug-like qualities. Although hepatotoxicity was expected and requires further experimental validation, the overall pharmacokinetic profile shows that these compounds are viable for future medication development. This computational analysis suggests that coumarin-triazole-chalcone hybrid scaffolds are a suitable foundation for developing novel therapeutic drugs targeting α-amylase and α-glucosidase for diabetes control.

ACKNOWLEDGMENTS

The authors are grateful to Smt. Kamala and Sri Venkappa M. Agadi College of Engineering and Technology for providing the necessary research facilities.

Conflicts of Interest

There are no conflicts to declare.

REFERENCES

[1] M. Abdul Basith Khan, M.J. Hashim, J.K. King, R.D. Govender, H. Mustafa, J. Al Kaabi, Epidemiology of type 2 diabetes—global burden of disease and forecasted trends, Journal of epidemiology and global health, 10 (2020) 107-111.

[2] K.L. Ong, L.K. Stafford, S.A. McLaughlin, E.J. Boyko, S.E. Vollset, A.E. Smith, B.E. Dalton, J. Duprey, J.A. Cruz, H. Hagins, Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021, The Lancet, 402 (2023) 203-234.

[3] M.A. Nauck, J. Wefers, J.J. Meier, Treatment of type 2 diabetes: challenges, hopes, and anticipated successes, The lancet Diabetes & endocrinology, 9 (2021) 525-544.

[4] A. Kanwal, N. Kanwar, S. Bharati, P. Srivastava, S.P. Singh, S. Amar, Exploring new drug targets for type 2 diabetes: success, challenges and opportunities, Biomedicines, 10 (2022) 331.

[5] F. Khan, M.V. Khan, A. Kumar, S. Akhtar, Recent advances in the development of alpha-glucosidase and alpha-amylase inhibitors in type 2 diabetes management: insights from in silico to in vitro studies, Current Drug Targets, 25 (2024) 782-795.

[6] N. Kaur, V. Kumar, S.K. Nayak, P. Wadhwa, P. Kaur, S.K. Sahu, Alpha-amylase as molecular target for treatment of diabetes mellitus: A comprehensive review, Chemical biology & drug design, 98 (2021) 539-560.

[7] A.M. Dirir, M. Daou, A.F. Yousef, L.F. Yousef, A review of alpha-glucosidase inhibitors from plants as potential candidates for the treatment of type-2 diabetes, Phytochemistry Reviews, 21 (2022) 1049-1079.

[8] A. Mushtaq, U. Azam, S. Mehreen, M.M. Naseer, Synthetic α-glucosidase inhibitors as promising anti-diabetic agents: Recent developments and future challenges, European journal of medicinal chemistry, 249 (2023) 115119.

[9] H. Kashtoh, K.-H. Baek, Recent updates on phytoconstituent alpha-glucosidase inhibitors: an approach towards the treatment of type two diabetes, Plants, 11 (2022) 2722.

[10] A. Jaggal, K.S. Katagi, M. Akki, V. Babagond, V. Kamat, S. Joshi, A click-chemistry based strategy for synthesizing coumarin piperazine analogues: Assessment of anti-tubercular, anti-cancer, anti-inflammatory and antioxidant potentials, Journal of Molecular Structure, 1320 (2025) 139388.

[11] M. Akki, D.S. Reddy, K.S. Katagi, A. Kumar, H.C. Devarajegowda, S. Kumari M, V. Babagond, S.D. Joshi, Coumarin Hydrazone Oxime Scaffolds as Potent Anti-tubercular Agents: Synthesis, X-ray crystal and Molecular Docking Studies, ChemistrySelect, 7 (2022) e202203260.

[12] S. Khatoon, R. Naaz, U. Khan, F. Qayyum, S. Ahmad, M. Saquib, M.K. Hussain, Natural coumarins as anti-diabetic agents: Mechanisms, therapeutic potential, and amelioration of diabetic complications, Phytomedicine, (2025) 157339.

[13] S. Ranđelović, R. Bipat, A review of coumarins and coumarin-related compounds for their potential antidiabetic effect, Clinical Medicine Insights: Endocrinology and Diabetes, 14 (2021) 11795514211042023.

[14] H. Li, Y. Yao, L. Li, Coumarins as potential antidiabetic agents, Journal of Pharmacy and Pharmacology, 69 (2017) 1253-1264.

[15] B. Debnath, S. Manna, A. Maity, S. Panda, K. Bandyopadhyay, S. Bhattacharjee, S. Khan, S.M. Islam, D. Thekkekkara, S.A. Khan, Synthetic Strategies and Structure Activity Relationships (SAR) of Biologically Active Coumarin-Based Hybrids, ChemistrySelect, 10 (2025) e202406069.

[16] Y. Pan, T. Liu, X. Wang, J. Sun, Research progress of coumarins and their derivatives in the treatment of diabetes, Journal of enzyme inhibition and medicinal chemistry, 37 (2022) 616-628.

[17] V. Babagond, K. Katagi, M. Akki, V. Kamat, D.A. Barretto, A. Jaggal, S. Kademani, A. Shirahatti, A Click chemistry approach for the synthesis of triazole linked vanillin scaffolds as potent pharmacophores: anti-diabetic, anti-inflammatory, antioxidant, molecular docking and admet investigations, Polycyclic Aromatic Compounds, 45 (2025) 1717-1740.

[18] A. Jaggal, K.S. Katagi, M. Akki, V. Babagond, V. Kamat, D.A. Barretto, S. Kademani, Design and synthesis of potent coumarin-1, 2, 3-triazole conjugates: An approach to docking studies for their therapeutic applications, Journal of Molecular Structure, (2025) 143519.

[19] A. Sharma, R. Dubey, R. Bhupal, P. Patel, S.K. Verma, S. Kaya, V. Asati, An insight on medicinal attributes of 1, 2, 3-and 1, 2, 4-triazole derivatives as alpha-amylase and alpha-glucosidase inhibitors, Molecular Diversity, (2023) 1-30.

[20] A. Singh, K. Singh, A. Sharma, U. Kaur, K. Kaur, P. Mohinder Singh Bedi, Recent developments in 1, 2, 3-triazole based α-glucosidase inhibitors: design strategies, structure-activity relationship and mechanistic insights, Chemistry & Biodiversity, 21 (2024) e202401109.

[21] S. Rocha, D. Ribeiro, E. Fernandes, M. Freitas, A systematic review on anti-diabetic properties of chalcones, Current medicinal chemistry, 27 (2020) 2257-2321.

[22] S. Welday Kahssay, G.S. Hailu, K. Taye Desta, Design, synthesis, characterization and in vivo antidiabetic activity evaluation of some chalcone derivatives, Drug Design, Development and Therapy, (2021) 3119-3129.

[23] S. Rocha, A. Sousa, D. Ribeiro, C.M. Correia, V.L. Silva, C.M. Santos, A.M. Silva, A.N. Araújo, E. Fernandes, M. Freitas, A study towards drug discovery for the management of type 2 diabetes mellitus through inhibition of the carbohydrate-hydrolyzing enzymes α-amylase and α-glucosidase by chalcone derivatives, Food & function, 10 (2019) 5510-5520.

[24] V. NAHOUM, G. ROUX, V. ANTON, P. ROUGÉ, A. PUIGSERVER, H. BISCHOFF, B. Henrissat, F. PAYAN, Crystal structures of human pancreatic α-amylase in complex with carbohydrate and proteinaceous inhibitors, Biochemical Journal, 346 (2000) 201-208.

[25] T. Tagami, K. Yamashita, M. Okuyama, H. Mori, M. Yao, A. Kimura, Molecular basis for the recognition of long-chain substrates by plant α-glucosidases, Journal of Biological Chemistry, 288 (2013) 19296-19303.

[26] H. Krishnapura Nagaraja Rao, V.B. Das, V. Kamat, M. Akki, B. Poojary, S. Gowdar, S. Asthana, M. Pareek, Design, Synthesis, and Fungicidal Activity of a New Class of Thiadiazolylpyrimidine Carboxamide Derivatives Against R. solani Kuhn, Chemistry & Biodiversity, 22 (2025) e01520.

[27] O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, Journal of computational chemistry, 31 (2010) 455-461.

[28] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Advanced drug delivery reviews, 23 (1997) 3-25.

[29] D.F. Veber, S.R. Johnson, H.-Y. Cheng, B.R. Smith, K.W. Ward, K.D. Kopple, Molecular properties that influence the oral bioavailability of drug candidates, Journal of medicinal chemistry, 45 (2002) 2615-2623.

[30] A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, Scientific reports, 7 (2017) 42717.