Bulletin of Pharmaceutical Research 2024;14(2):185

An Official Publication of Association of Pharmacy Professionals

ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)

DOI: 10.21276/bpr.2024.14.2.1

RESEARCH PAPER

IDENTIFICATION OF NEW CHEMICAL ENTITIES AS VHL INHIBITORS FOR DIABETIC WOUND HEALING

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Received: Dec 08, 2023 / Revised: Aug 28, 2024 / Accepted: Aug 28, 2024

Diabetes is a kind of endocrine disease that impacts around 6% of the world's population. Globally, 68% of amputations were performed in persons with diabetes. Hypoxia-inducible factor 1-alpha (HIF-1α) is a crucial regulator of wound healing in diabetic patients, which includes epithelialization, angiogenesis, granulation, tissue development, and wound contraction. Even though diabetic wounds are hypoxic, HIF-1α levels are decreased during diabetic conditions. Diabetic wound healing necessitates the modulation of hypoxia-induced responses by VHL–HIF-1α protein-protein inhibition (PPI). Our proposed hypothesis is to increase HIF-1α levels by inhibiting VHL and HIF-1α interactions by small bioactive molecules, accelerating diabetic wound healing. Three features (Two hydrogen bond acceptors and One hydrogen bond donor) pharmacophore model was generated from the existing VHL inhibitors. Virtual screening was done based on the generated pharmacophore, and a library of 700 compounds was selected using ZINCPharmer. Based on the docking analysis the Top 15 HITs were selected & after performing ADMET studies, the Top 2 HITs (ZINC04214700 and ZINC12529886) were identified as potential VHL inhibitors. From this finding, we demonstrated that inhibiting the VHL and HIF-1α connection is a promising strategy for treating diabetic wounds.

Key words: Diabetic wound, HIF-1α, VHL, PPI, Pharmacophore, Virtual screening, Docking, ADMET.

INTRODUCTION

Diabetes is a most common, serious and chronic illness resultant from the error of insulin secretions or action. The possible way of the treatment includes gene therapy, use of biguanides, GLP-1 receptor agonists, PPARγ agonists, including naturally occurring phenolic compounds. This metabolic disease is a significant risk factor for the development of chronic wounds, including foot ulcers, which can lead to severe complications such as amputation, decreased quality of life, and increased healthcare costs. According to the World Health Organization (WHO), an estimated 422 million people worldwide had diabetes in 2014, and this number is projected to increase to 642 million by 2040 and up to 25% of individuals with diabetes will develop a foot ulcer in their lifetime [1-8]. HIF-1α is crucial for enhancing the right inflammatory and angiogenic responses in normal cutaneous wounds. HIF-1α also plays a crucial role in controlling inflammatory reactions, one of the most common causes of

tissue hypoxia, in line with its function in mediating adaptation to hypoxia. Low oxygen concentrations are present around exterior wounds, inflamed tissues, and other places. Through its management of the metabolic switch to glycolysis, HIF-1α can affect the cellular inflammatory reaction. HIF-1α activation is also a primary stimulus of angiogenesis, the formation of new blood vessels from pre-existing vessels, in both physiological and pathological conditions [9]. HIF-1α is targeted for proteasomal degradation by the tumor suppressor protein von Hippel-Lindau (VHL), which binds to HIF-1α in its hydroxylated form. HIF-1α has been extensively studied and has been shown to play a critical role in the multistage process of wound healing. In essence, the expression of numerous angiogenic growth factors, cell motility, and the attraction of endothelial progenitor cells depend on HIF-1α [10].

HIF-1α stabilizers are a promising new class of drugs that have shown potential in promoting wound healing in diabetic conditions [11]. Several compounds have been identified as HIF-1A stabilizers that can activate or stabilize HIF-1α resulting in improved wound healing, thereby inducing its transcriptional activity even in normoxic conditions. One such compound is cobalt chloride ($CoCl_2$), which is a chemical mimic of hypoxia that can activate HIF-1α by inhibiting the activity of prolyl hydroxylases (PHDs), enzymes that hydroxylate and target HIF-1α for degradation. Another compound, dimethyloxalylglycine (DMOG), is also a PHD inhibitor that stabilizes HIF-1α by preventing its degradation. FG-4592 is an oral HIF-1α stabilizer that works by inhibiting PHD activity, leading to HIF-1α accumulation and activation. Similarly, deferoxamine (DFO) is an iron chelator that stabilizes HIF-1α by preventing hydroxylation and subsequent degradation [12]. The activation or stabilization of HIF-1α by these compounds has shown potential for therapeutic use in various diseases, including cancer, ischemic injury, and wound healing. All of the medications, stabilize HIF-1α by blocking PHD. PHD inhibitors have been limited by low target selectivity and adverse side effects, despite having entered clinical trials for disorders associated to angiogenesis [13]. In a phase 2 clinical study, for example, FG-2216 was associated with liver abnormalities, and one patient experienced fatal hepatic necrosis [14]. A further tactic to prevent HIF-1α degradation is to restrict the downstream connection between HIF-1α and the Von Hippel-Lindau tumor suppressor (VHL) protein, which is a negative regulator of HIF-1α (**Figure 1**). In addition, it has been reported that VH298 the most potent *in vitro* VHL-HIF-1α protein-protein interaction (PPI) inhibitor identified to date selectively stabilizes hydroxylated HIF-α and encourages in vivo wound and enthesis healing [15, 16]. In addition to VH298, our group recently reported a small molecule VHL-HIF-1α PPI inhibitor as a promising agent for wound healing *in vivo* [11].

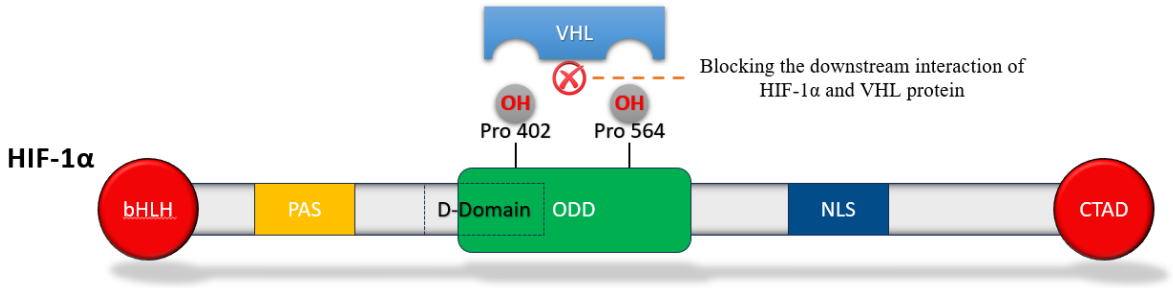


Fig. 1. HIF-1α:VHL PPI inhibition pathway

Several recent success stories indicate that protein-protein interfaces might be more efficient. Some studies discovered small molecules that bind with drug-like potencies to 'hotspots' on the contact surfaces involved in protein-protein interactions. Remarkably, these small molecules bind deeper within the contact surface of the target protein and bind with much higher efficiencies than the contact atoms of the natural protein partner. There is much interest in targeting the interfaces between interacting proteins for therapeutic purposes [17]. However, studying the efficacy and safety of these drugs in a laboratory setting can be time-consuming and expensive. In recent years, *in silico* studies have emerged as a powerful tool for predicting the properties of drug molecules and their potential therapeutic effects. In this context, we use several software programs such as PharmaGist, ZINCPharmer, PyRx, Discovery Studio,

SwissADME, and PreADMET have been developed that allow for the virtual screening of drug molecules and prediction of their pharmacological properties [18]. We use these programs to study the molecular interactions of VHL inhibitors with their target proteins and to predict their pharmacokinetic and toxicity profiles. In this research work, we will explore the use of these *in-silico* studies in the investigation of the diabetic wound healing properties of VHL inhibitors, highlighting their potential benefits towards the Diabetic wound healing treatment [19].

MATERIALS AND METHODS

Pharmacophore modeling

PharmaGist is a web server that provides a user-friendly interface for pharmacophore modelling and virtual screening. It is designed to generate pharmacophore hypotheses based on the known ligands of a target protein and can be used for ligand-based drug design [20]. The process of using PharmaGist begins with uploading a set of 23 ligands that have known binding affinities to the target protein (4W9H) in MOL2 format. These ligands are chosen to represent a diverse range of chemical structures obtained from various studies, which helps to ensure that the generated pharmacophore model is capable of accommodating a wide range of chemical compounds. When filling in the required information for your job on the PharmaGist webserver, we need to provide your email address where we want to receive the results. This is important as the webserver will send you an email notification when our job is finished with a link to download the results [21].

Virtual screening

Virtual screening is a computational technique used in drug discovery to search libraries of small molecules in order to identify those structures which are most likely to bind to a drug target, typically a protein receptor or enzyme. ZINCPharmer is an online interface for searching the purchasable compounds of the zinc database using Pharmer pharmacophore search technology [22]. ZINCPharmer identifies hydrophobic, hydrogen bond donor/acceptor, positive/negative ions and aromatic pharmacophore features using the SMARTS matching functionality of the Open Babel toolkit. Additional property filters, such as molecular weight, may be specified under the Filters tab while the visual styles of the molecular viewer also used. The results browser is on the right and displayed 700 ZINC id, which links directly to the ZINC database and purchasing information, the minimal RMSD of the compound pose to the query, the molecular weight and the number of rotatable bonds.

Molecular docking

We have utilized PyRx 0.8 to dock 700 molecules, including the co-crystal, against a protein (4w9h) prepared using Discovery Studio. To begin, the protein was loaded into PyRx and converted into a macromolecule. Then, the molecules to be docked were loaded one by one using the inbuilt Open Babel tool and minimized to remove any steric clashes. These minimized molecules were then converted into ligands for docking [23].

For docking, Vina Wizard was used. The protein macromolecule and all the ligands were selected, and the active site of the protein was focused on based on information from the Protein-Ligand Interaction Profiler. This helps to identify potential binding sites on the protein by analyzing the interaction between the protein and ligand. The docking results were obtained based on the binding affinity, which is a measure of how tightly the ligand binds to the protein. The top molecules were selected based on their binding affinity and are expected to have the highest potential to interact with the protein and potentially act as drug candidates. Our study utilized PyRx 0.8, Discovery Studio, Open Babel, and Vina Wizard to dock and screen 700 molecules against a protein of interest, identifying top candidates based on binding affinity [24, 25].

ADMET studies

ADMET studies evaluate the pharmacokinetics and safety profile of drug candidates, covering absorption, distribution, metabolism, excretion, and toxicity. Absorption studies focus on how the drug enters the bloodstream, while distribution studies examine its transport and accumulation in organs and tissues. Metabolism studies investigate breakdown of drug and its metabolites, and excretion studies assess elimination through kidneys and liver. Toxicity studies evaluate the potential side effects, guiding decision-making during the drug development. ADMET studies require a multi-disciplinary approach and are essential for evaluating the drug candidate safety and efficacy [26].

SwissADME

SwissADME is a web-based tool that offers an efficient and comprehensive platform for predicting the pharmacokinetic and physicochemical properties of small molecules. SwissADME employs several algorithms and models, including Lipinski's Rule of Five, Ghose Filter, Veber Rule, Muegge Rule, and PAINS Filter. These algorithms and models are used to predict a variety of ADME and physicochemical properties of small molecules [27]. For instance, Lipinski's Rule of Five is a popular filter used to predict the likelihood of a compound to have good oral bioavailability based on its molecular weight, lipophilicity, number of hydrogen bond donors and acceptors, number of rotatable bonds, and polar surface area. SwissADME also includes various physicochemical property calculators, such as LogP (octanol-water partition coefficient), polar surface area, and number of H-bond donors and acceptors [28].

Pre ADMET

Pre ADMET is a web-based application for predicting ADME data, Toxicity profile and building drug-like library using *in silico* method. Drug-Likeness Prediction (Lipinski's rule, lead-like rule, Drug DB like rule), ADME Prediction (Caco-2, MDCK, BBB, HIA, plasma protein binding and skin permeability data), Toxicity Prediction (Ames test and rodent carcinogenicity assay). It has three modules namely: Drug-likeness prediction, ADME prediction and Toxicity prediction. Either load the structure or draw it in the box provided and click submit to obtain the characteristics of the molecule [29].

RESULTS AND DISCUSSION

In silico studies

Pharmacophore modeling

In this study, we employed PharmaGist to generate pharmacophore models for a set of 23 compounds known to bind to the target protein of interest (4W9H). We obtained few pharmacophore models, which were ranked based on their fit scores. The top-ranked of three features two HBA and one HBD.

Input

The input for PharmaGist includes the 3D structure of ligands, their corresponding activity values, and the structure of the target protein. In our study, we used a set of 23 compounds with known binding affinity to the target protein. The ligands were prepared from PubChem and converted to mol2 format using open babel, which generates low-energy conformations and protonation states for each ligand. The ligand structures were then optimized.

Output

The output of PharmaGist includes a set of pharmacophore models that represent the common features among the ligands responsible for binding to the target protein. In our study, we obtained a few pharmacophore models, The top-ranked of three features Pharmacophore model which consist of two HBA and one HBD which were ranked based on their fit scores. The fit score is a measure of the overall similarity between the pharmacophore model and the ligands used to generate it. The higher the fit score, the better the model is at representing the common features among the ligands. It is then downloaded as jmol file shown in **Figure 2**.

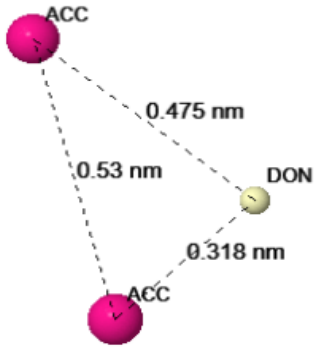


Fig. 2. Pharmacophore model

Virtual screening

Using a Web-based query tool with a molecular sketching interface, the data can be searched, analyzed, and subgroups can be created. Users have the option to process their own molecules after uploading them to a server. We hope that this tool will be utilized by a sizable community of structural biologists and medicinal chemists to build virtual screening libraries. The ZINCPharmer application offers several filters that can be used to restrict down the database's chemicals based on pharmacophoric properties. Due to different mappings of query attributes to ligand properties, Max Hits per Conf is used to limit the number of conformer orientations returned. This filer is required for exceedingly symmetric searches with an unlimited number of possible positions.

Molecular maximum hits

This parameter restricts the amount of hits for the same chemical that are returned.

RMSD's statistical significance

The forecast is usually successful if the RMSD is less than 2 Å. The obvious goal is to make this "near-native" approach the most popular ligand position. As a result, we filtered the 700-Ligand in this study by making the highest RMSD value not more than 2. Sort the Daltons by their molecular weight (value includes hydrogens). The 700-Ligandwasfilteredin this study by reducing the Molecular Weight value to less than 500 Dalton. Rotatable Bonds: Sort by how many rotatable bonds there are. The SMARTS expression is used to identify rotatable bonds. The virtual screening was performed using the generated pharmacophore in ZINCPharmer (**Figure 3**). For present research, the natural product database is chosen. The pharmaGist's pharmacophore data is used to perform virtual screening. Based on the natural product database, ZINCPharmer generated 3782 hits. 700 compounds are chosen based on their RMSD and 15 compounds are chosen for docking investigations based on drug-likeness, according to ADMET.

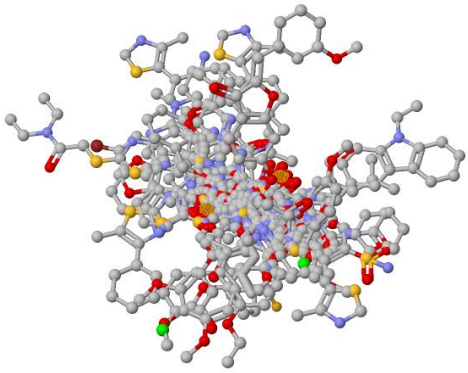


Fig. 3. Generated pharmacophore in ZINCPharmer

Molecular docking

Preparation of protein and identification of the active sites

The protein's 3D structure was obtained from the Protein Data Bank (PDB: 4W9H). The active site amino acid residues were identified based on the protein-ligand interaction profile (PLIP). TRP 88, THR 98, ILE 109, HIS 110, TYR 112, TYR 115 are the amino acid residues found in a catalytic pocket. The Ramachandran plot, as shown in **Figure 4**. was used to validate the prepared protein.

Docking in PyRx

PyRx was used to choose the best "15 HITS" from 700 molecules identified from virtual screening and co-crystal was taken as standard.

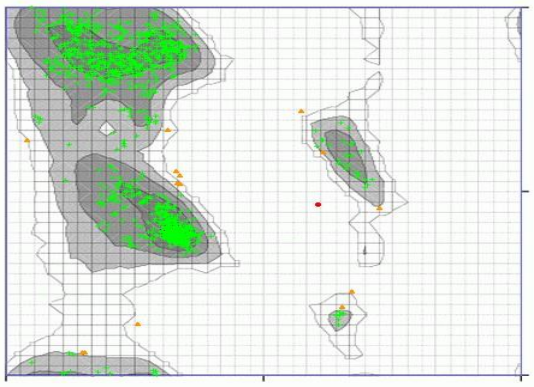


Fig. 4. Ramachandran plot

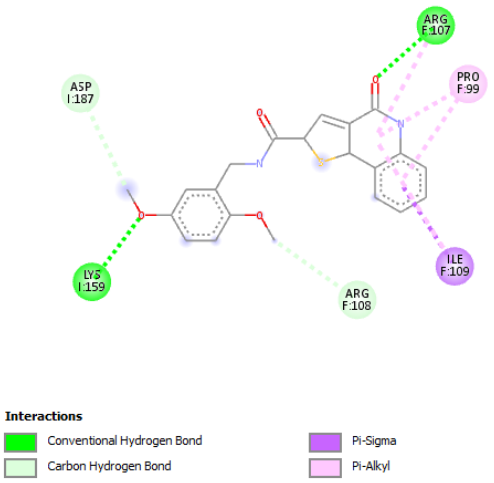
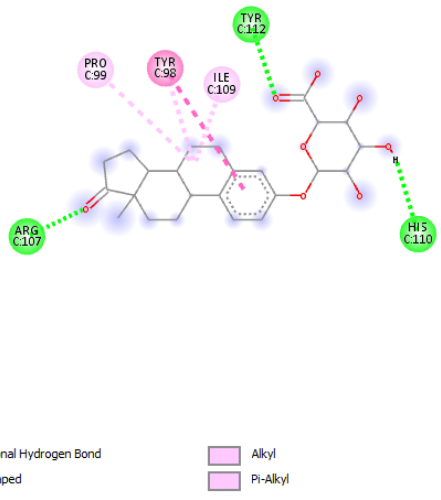
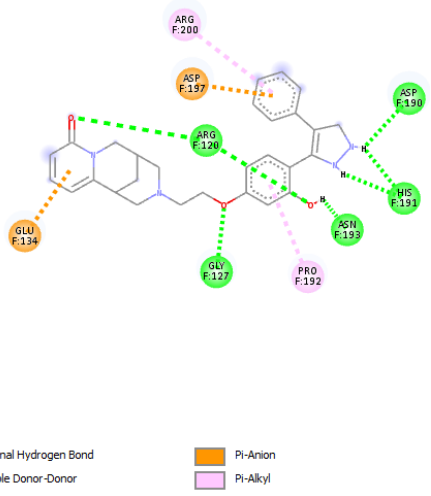
PyRx binding energy refers to the interaction energy between the protein and the ligand. This RMSD value reflects the level of interaction between proteins and ligands. The inclusion of the compounds 2D interactions with greater binding energies (co-crystals) in the **Table 1**. demonstrates how effectively the compounds bound to the VHL protein's active site (4W9H). Investigations into these compounds' interactions with VHL protein.

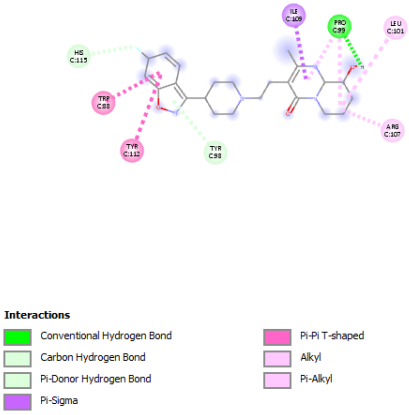
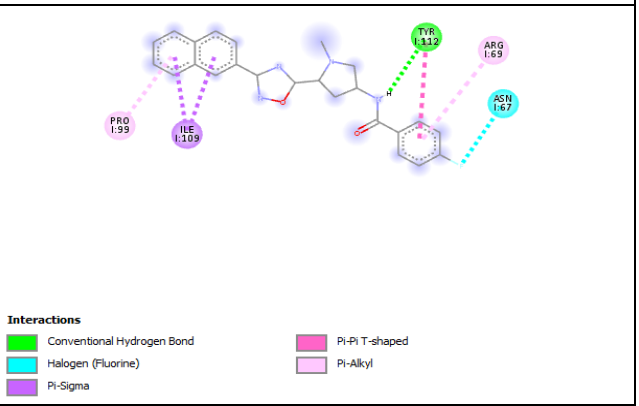
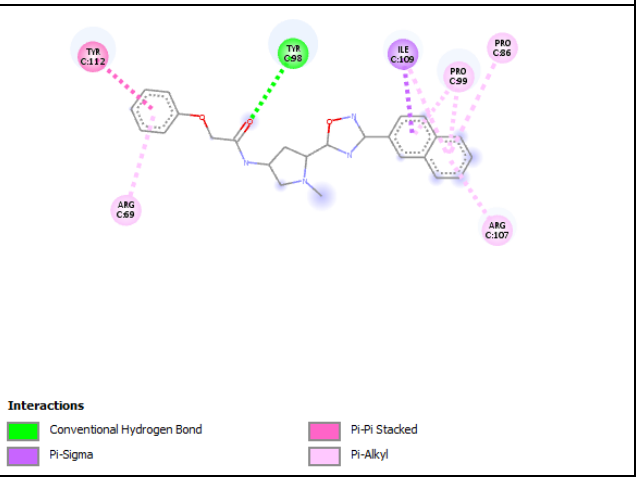
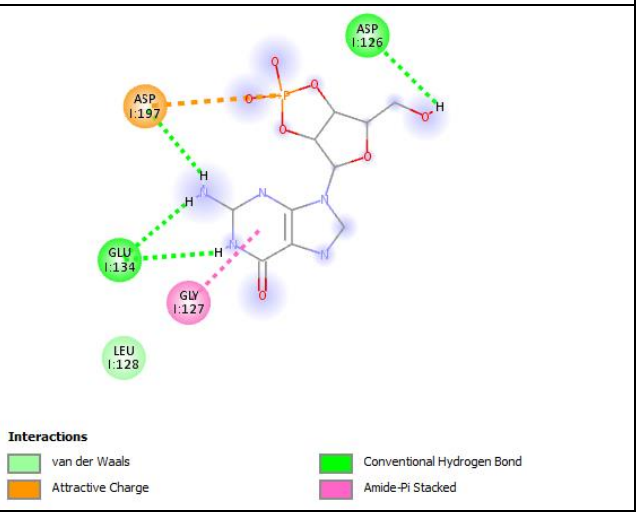
ADMET studies

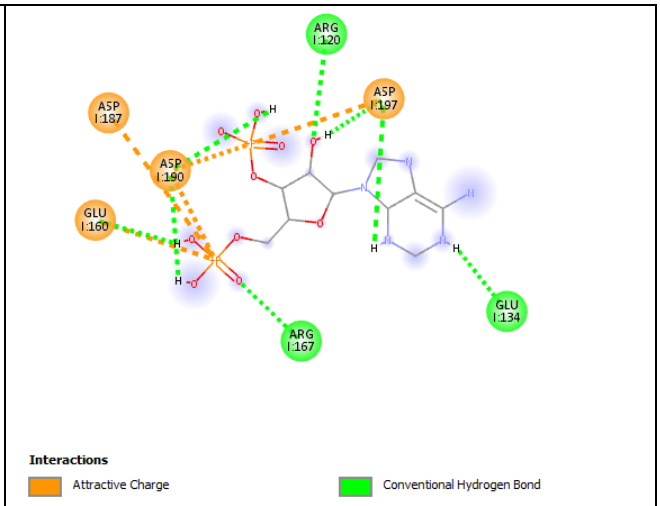
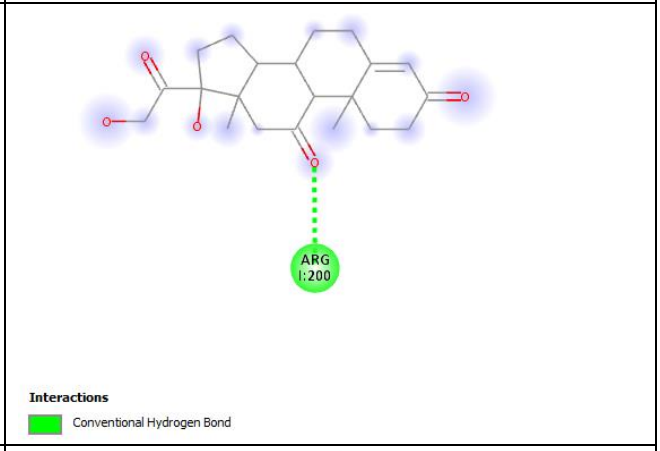
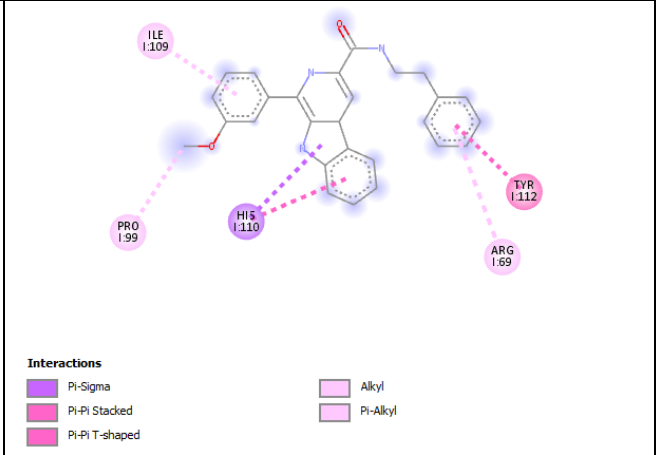
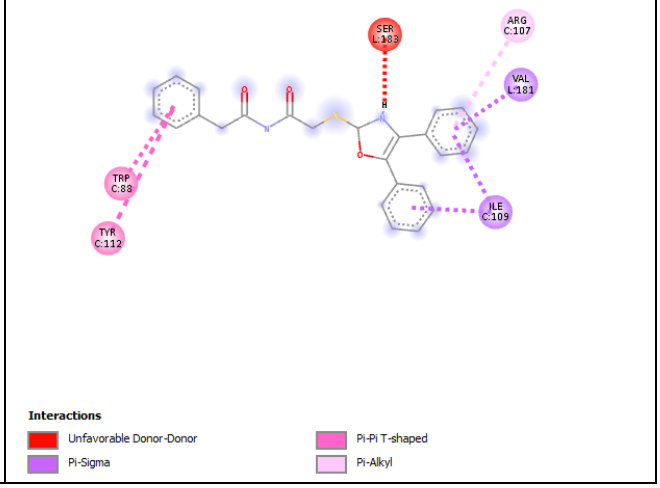
In silico ADMET studies

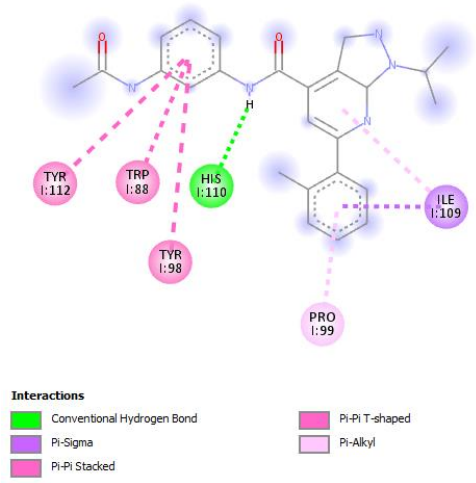
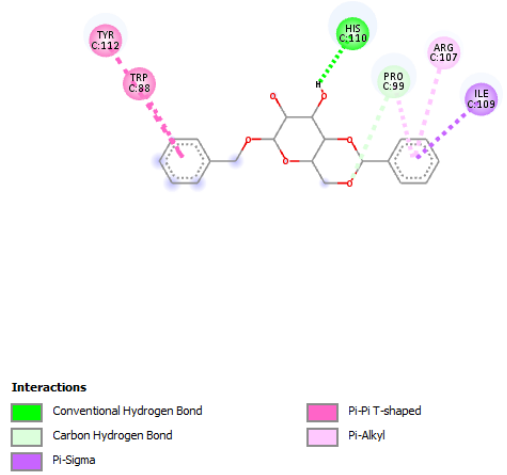
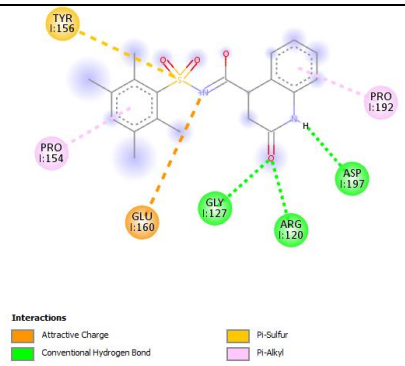
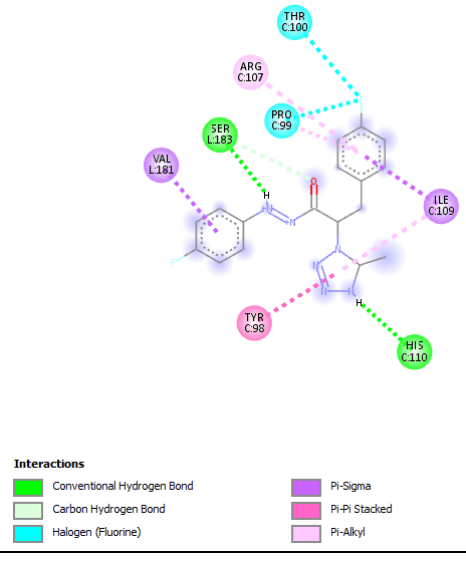
The drug likeness of selected compounds was determined by evaluating the physicochemical and pharmacokinetic properties using Swiss ADME and the results were tabulated in the **Table 2** and **Table 3**. The aqueous solubility is considered as most important for considering the bioavailability of the drug. In connection with this, the molecules 7 and 8 were highly soluble, molecules ZINC63479135, ZINC0409 9004, ZINC04214700, ZINC03830599, ZINC3860 0479, ZINC69604154 were soluble and molecules ZINC08791878, ZINC12529886, ZINC12529888, ZINC05932590, ZINC08824143, ZINC14211067, ZINC79450121 were moderately soluble. XlogP3 computes the lipophilicity of molecule and represents partition coefficient values of compounds in permeability, distribution, and clearance route of drugs. This parameter also plays an essential role in pharmacological and toxic properties of drugs. XlogP3 values for all the molecules were within the required limit below five except ZINC05932590, ZINC08824143, ZINC79450121 which had XlogP3 values 5.05, 5.13 and 5.07 respectively. The polar surface area of the compound is in an inverse relationship with human intestinal absorption and all selected molecules exhibited values less than 200 except molecule 8 and thus except molecule 8, all others

Table 1. Binding affinity and 2D interactions of top HITS

Name of the compound	Binding energy (kcal/mol)	2D-Interaction
ZINC63479135	-7.8	
ZINC04099004	-8	
ZINC08791878	-9	

ZINC04214700	-9.9	
ZINC12529886	-9.9	
ZINC12529888	-9.1	
ZINC04097050	-7.9	

ZINC03869248	-7.7	
ZINC03830599	-7.8	
ZINC05932590	-9	
ZINC08824143	-9.2	

ZINC14211067	-9.6	
ZINC38600479	-8.8	
ZINC69604154	-8.9	
ZINC79450121	-8.6	

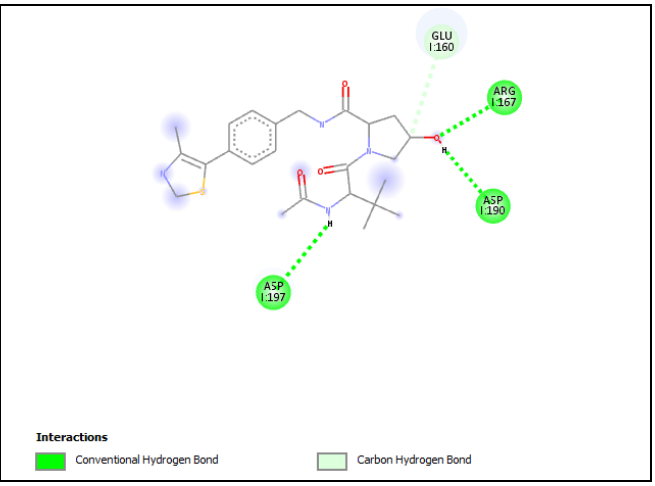
CO-CRYSTAL	-7.4	

Table 2. Molecular properties of compounds

Name of compound	Molecular weight	nrtob	H-bond acceptors	H-bond donors	Molar refractivity	TPSA
ZINC63479135	395.45	6	4	2	109.98	112.51
ZINC04099004	446.49	3	8	4	112.66	136.35
ZINC08791878	470.56	6	5	3	147.89	78.76
ZINC04214700	430.52	4	6	3	129.45	77.07
ZINC12529886	416.45	5	5	3	124.04	67.32
ZINC12529888	428.48	7	5	3	130.19	76.55
ZINC04097050	348.23	2	8	6	84.86	177.45
ZINC03869248	433.25	6	12	9	99.43	247.95
ZINC03830599	360.44	2	5	2	96.57	91.67
ZINC05932590	423.51	7	2	3	133.29	62.39
ZINC08824143	430.52	9	3	2	126.81	92.73
ZINC14211067	431.53	7	3	4	138.84	85.5
ZINC38600479	358.39	4	6	2	91.98	77.38
ZINC69604154	388.48	4	5	3	107.79	103.88
ZINC79450121	360.36	7	5	3	105.3	81.12

Table 3. Pharmacokinetic properties of the compounds

Molecule	XLOGP3	GI abs.[1]	BBB perm.[2]	CYP2D6 inhibitor	Lipinski violations	PAINS alerts	Synth. Access.[3]	CYP3A4 inhib.[4]	CYP2C9 inhib.
ZINC63479135	2.52	High	No	No	0	0	4.18	No	No
ZINC04099004	1.57	High	No	Yes	0	0	5.41	No	No
ZINC08791878	2.97	High	No	Yes	0	0	5.29	Yes	Yes
ZINC04214700	2.32	High	No	Yes	0	0	5.43	No	No
ZINC12529886	3.4	High	Yes	Yes	0	0	4.36	No	No
ZINC12529888	3.34	High	Yes	Yes	0	0	4.47	Yes	Yes
ZINC04097050	-5.19	Low	No	No	2	0	5.14	No	No
ZINC03869248	-9.7	Low	No	No	2	0	5.55	No	No
ZINC03830599	1.47	High	No	No	0	1	5.07	No	No
ZINC05932590	5.05	High	Yes	Yes	0	0	4.46	Yes	Yes
ZINC08824143	5.13	High	No	Yes	0	0	4.38	Yes	Yes
ZINC14211067	2.95	High	No	Yes	0	0	4.9	Yes	Yes
ZINC38600479	1.36	High	No	Yes	0	0	4.77	No	No
ZINC69604154	2.46	High	No	No	0	0	3.89	Yes	No
ZINC79450121	5.07	High	No	No	0	0	3.96	Yes	Yes

[1]Gastrointestinal absorption; [2]Blood Brain Barrier permeations; [3]Synthetic accessibility; [4]CYP3A4 inhibition

were predicted to have high absorption. Usually most of the drugs must not pass the blood brain barrier if the target is not related to the nervous system. All the selected molecules ADME

properties were in the acceptable limits shown in the egg model (**Figure 5**). The total numbers of rotatable bonds are 2-9, which shows the flexibility of all the selected molecules. Except molecules ZINC04097050, ZINC03869248 all other molecules were obeying Lipinski rule of five. Molecules ZINC63479135, ZINC12529886, ZINC12529888, ZINC05932590, ZINC08824143, ZINC14211067, ZINC38600479, ZINC69604154, ZINC79450121 had synthetic accessibility score between 3.5 and 5 which means the synthesis accessibility is moderately easy and molecules ZINC04214700, ZINC04097050, ZINC03869248, ZINC03830599 had the synthetic accessibility score between 5 and 5.6 which means the synthesis is moderately difficult.

A super family gene member of human cytochrome P450 enzyme is versatile one and could metabolize the various hydrophobic compounds through its oxidation and eventually remove the foreign compounds. Among this major family of CYPs, the three isoforms *viz.* 2D6, 2C9, and 3A4 are considered more important and responsible for microsomal oxidation of most drugs in the human body. CYP2D6 metabolize more than 27.5% of drugs, CYP3A4 is responsible for metabolizing more than 50% of the drugs and CYP2C9 metabolizes approximately 20% of the drugs. The molecules ZINC08791878, ZINC12529888, ZINC05932590, ZINC08824143, ZINC14211067, ZINC69604154, ZINC79450121 inhibited CYP3A4. The molecules ZINC08791878, ZINC12529888, ZINC05932590, ZINC08824143, ZINC14211067 inhibited CYP2C9 and the molecules ZINC04099004, ZINC08791878, ZINC04214700, ZINC12529886, ZINC12529888, ZINC05932590, ZINC08824143, ZINC14211067, ZINC38600479 inhibited CYP2D6. Hence the molecules ZINC04099004, ZINC08791878, ZINC04214700, ZINC12529886, ZINC12529888, ZINC05932590, ZINC08824143, ZINC14211067, ZINC38600479, ZINC69604154 and ZINC79450121 may cause serious drug interaction toxicity.

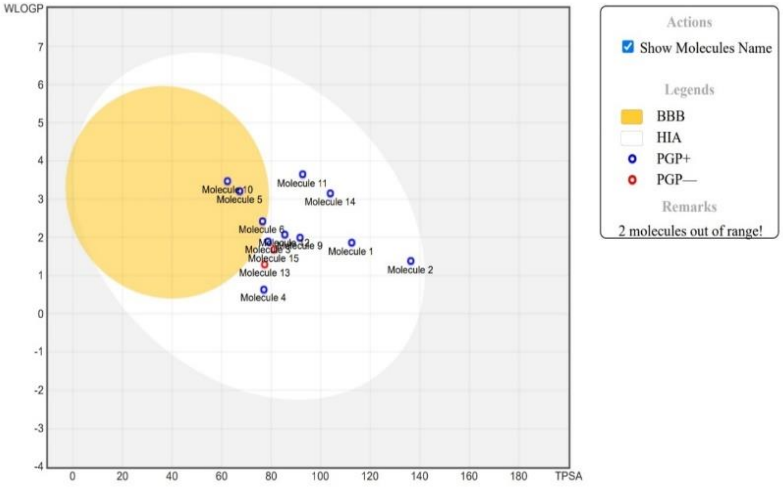


Fig. 5. SwissADME egg model

PreADMET results

The results of preADMET tests for Top HITs show that these compounds have low toxicity and are non-mutagenic which are shown in **Table 4**. The Algae test indicates that the compounds have low potential for environmental toxicity, with all values less than 0.03. The Ames test, which is used to assess the mutagenicity of a compound, showed that these compounds were non-mutagenic, indicating that we are safe for human consumption. The hERG inhibition test measures the ability of a compound to block the (hERG), which can cause cardiac arrhythmias.

The results show that these compounds have low-risk hERG inhibition, indicating that we are unlikely to cause adverse cardiac effects. The TA100_10RLI and TA1535_10RLI tests assess the potential of a compound to cause bacterial mutations.

All of the tested compounds showed negative results, which means we do not have mutagenic potential. The TA1535_NA test, which assesses the ability of a compound to cause gene mutations in bacteria, also showed negative results, further confirming the non-mutagenic properties of these compounds.

Finally, the Daphnia test measures the potential of a compound to cause acute toxicity to aquatic organisms. The results show that the compounds have low toxicity to Daphnia, with values ranging from 0.01 to 0.62.

Table 4. Toxicity studies for designed compounds

Sample code	Algae test	Ames test	hERG inhibition	TA100_10RLI	TA1535_10RLI	TA1535_NA	Daphnia
ZINC63479135	0.00144202	Non-mutagen	Low risk	negative	negative	negative	0.00569073
ZINC04099004	0.00237045	Non-mutagen	Low risk	negative	negative	negative	0.0111477
ZINC08791878	0.00257791	Non-mutagen	Low risk	negative	negative	negative	0.01631
ZINC04214700	0.00237295	Non-mutagen	Low risk	negative	negative	negative	0.0107329
ZINC12529886	0.0282117	Non-mutagen	Low risk	negative	negative	negative	0.598832
ZINC12529888	0.007862	Non-mutagen	Low risk	negative	negative	negative	0.016886
ZINC04097050	0.00963572	Non-mutagen	Low risk	negative	negative	negative	0.029567
ZINC03869248	0.0007356	Non-mutagen	Low risk	negative	negative	negative	0.526733
ZINC03830599	0.0456843	Non-mutagen	Low risk	negative	negative	negative	0.013657
ZINC05932590	0.0085679	Non-mutagen	Low risk	negative	negative	negative	0.065892
ZINC08824143	0.059354	Non-mutagen	Low risk	negative	negative	negative	0.135127
ZINC14211067	0.075632	Non-mutagen	Low risk	negative	negative	negative	0.027612
ZINC38600479	0.015886	Non-mutagen	Low risk	negative	negative	negative	0.625795
ZINC69604154	0.004865	Non-mutagen	Low risk	negative	negative	negative	0.082647
ZINC79450121	0.025461	Non-mutagen	Low risk	negative	negative	negative	0.086579

CONCLUSION

There is an urgent need to speed up research in this field in order to find treatment for diabetic wound healing. HIF1α signaling can be a pharmacological target for disorders associated with angiogenesis, as shown in clinical trials by the efficiency of PHD inhibitors. However, PHDs inhibitors have a few drawbacks, such as a lack of target specificity and potentially harmful side effects. There were aberrant liver enzyme test results in a Phase 2 trial with FG-2216 and one patient died of hepatic necrosis. A new class of VHL inhibitors has been created as an alternative to conventional PHDs inhibitors. At the end of the study, we have identified top 15 compounds from a dataset of 700 compounds through various molecular modeling tools such as pharmacophore modeling, virtual screening and molecular docking. The ADMET studies were performed for top 15 compounds and all the identified compounds are safe to administer. Two effective molecules ZINC04214700 and ZINC12529886 are developed at the end of this study as VHL inhibitors and identified as potential candidates for the treatment of diabetic wound.

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