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In silico Design and Computational Assessment of Small-Molecule GLP-1R Agonist as a Possible Treatment for Obesity and Type 2 Diabetes

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Abstract

Obesity is one of the most concerning health hazards in recent years as it associated with a large number of diseases such as diabetes mellitus. Glucagon-like peptide-1 receptor agonists are clinically tested treatment options for obesity along with type 2 diabetes. We present the rational *in silico* design and computational assessment of ThiaGlip-1, an innovative small-molecule GLP-1R agonist candidate based on a previously unreported indolo[1,2-b]quinoxaline tetracyclic framework. A Tanimoto similarity of 0.41 compared to the closest known analogue confirming that the structure is new. By using Auto Dock Vina 1.2.3 to do molecular docking toward active-state GLP-1R, it was found that ThiaGlip-1 had the best binding affinity of −9.222 kcal/mol, which is similar to the reference agonist Danuglipron (−9.763 kcal/mol). After that, a virtual library of similar compounds was generated via Swiss Similarity. Virtual screening of 380 Enamine_Tang library compounds found 294 candidates (77.4%) with Excellent binding affinity. The best compound had a binding affinity of −12.931 kcal/mol. The SAR analysis found that LogP, the number of aromatic rings, and the number of heavy atoms were the main factors that affected GLP-1R binding affinity. ADMET profiling demonstrated that 270 library compounds (71.1%) have no toxicity flags and a mean drug score of 1.00. The three best leads, Z4594432747, PV-002918833325, and PV-004003938144, were chosen as the best candidates for further experimental follow-up to be framework for a new orally active anti-obesity and antidiabetic drugs in the future.

تصميم وتقييم حاسوبي لجزيء صغير محفز لمستقبلات الببتيد الشبيه بالجلوكاجون-1 كعلاج محتمل للسمنة ومرض السكري من النوع الثاني

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فرع الكيمياء الصيدلانية, كلية الصيدلة, جامعة الموصل, موصل, عراق

الخلاصة
تُعدّ السمنة من أخطر المخاطر الصحية في السنوات الأخيرة لارتباطها بالعديد من الأمراض، مثل داء السكري. وتُعتبر مُحفزات مستقبلات الببتيد الشبيه بالجلوكاجون-1 خيارات علاجية مُختبرة سريريًا للسمنة وداء السكري من النوع الثاني. نعرض هنا التصميم المنطقي والتقييم الحاسوبي لـ ThiaGlip-1، وهو مُحفز جزيئي صغير مُبتكر لمستقبلات GLP-1R، يعتمد على هيكل رباعي الحلقات من الإندولو[b-1,2]كوينوكسالين لم يُنشر عنه سابقًا. وقد أظهرت النتائج تشابهًا في معامل تانيموتو بنسبة 0.41 مع أقرب نظير معروف، مما يؤكد حداثة التركيب. عند استخدام برنامج AutoDock Vina 1.2.3 لإجراء محاكاة الارتباط الجزيئي مع مستقبلات GLP-1R في حالتها النشطة، وجدنا أن ThiaGlip-1 يتمتع بأفضل ألفة ارتباط بلغت -9.222 كيلو كالوري/مول، وهي قيمة مُشابهة للمُحفز المرجعي Danuglipron (-9.763 كيلو كالوري/مول). بعد ذلك، تم إنشاء مكتبة افتراضية لمركبات مشابهة باستخدام برنامج SwissSimilarity. أسفر الفحص الافتراضي لـ 380 مركباً من مكتبة Enamine_Tang عن تحديد 294 مرشحاً (77.4%) يتمتعون بألفة ارتباط ممتازة. وكان أفضل مركب يتمتع بألفة ارتباط قدرها -12.931 كيلو كالوري/مول. أظهر تحليل العلاقة بين التركيب والنشاط أن معامل التوزيع (LogP)، وعدد الحلقات الاروماتية، وعدد الذرات الثقيلة هي العوامل الرئيسية المؤثرة على ألفة ارتباط مستقبلات GLP-1R. وأظهر تحليل خصائص الامتصاص والتوزيع والاستقلاب والإخراج والسمية (ADMET) أن 270 مركباً من المكتبة (71.1%) لا تحمل أي مؤشرات سمية، وأن متوسط درجة الدواء فيها هو 1.00. تم اختيار أفضل ثلاث مركبات رائدة، وهي Z4594432747 وPV-002918833325 وPV-004003938144، كأفضل المرشحين لمزيد من المتابعة التجريبية، وذلك لتكون بمثابة إطار عمل لأدوية جديدة فعالة عن طريق الفم لعلاج السمنة والسكري في المستقبل.

الكلمات المفتاحية: السمنة؛ داء السكري من النوع الثاني؛ محفزات GLP-1R ؛ الالتحام الجزيئي ؛ تحليل العلاقة بين التركيب والنشاط ؛ تحليل خصائص الامتصاص والتوزيع، والاستقلاب، والإخراج، والسمية.

INTRODUCTION

Overweight, or obesity, is a chronic condition with a body mass index ≥ 30, resulting from excess fat buildup in the adipose tissue in the body. It is commonly influenced by number of causes including inherited characteristics, neurobiological characteristics, and bad dietary habits [1,2]. The glucagon-like peptide-1 receptor, or GLP-1R, is a type of G-protein-coupled receptors (GPCRs) that is located in many organs inside the body mainly the pancreas, along with gastrointestinal tract, and central nervous system. It binds to the GLP-1 hormone to maintain blood sugar levels stable by making insulin more available so increase satiety [3,4].

GLP-1R agonists are a modern drug class that can help overweight as well as diabetic people to control their disease. When glucose levels are elevated, they stop glucagon release, slow down the gastric emptying, and help people lose a lot of weight with a low risk of hypoglycemia [5]. The emergence of small-molecule GLP-1R agonists is attracting significant research attention [6]. Some non-peptide chemotypes that have been presented to be GLP-1R agonists are substituted quinoxalines, fluoropyrimidines like Danuglipron, phenylalaninol derivatives like Orforglipron, and the cyclopentane scaffold Boc-5. Only two drugs were FDA approved orally active agents, even though, the newness of the reported orally active scaffolds' structures is still limited [7–15].

Molecular docking and virtual screening have become essential tools in structural based drug development. They let researchers quickly narrow down candidate compounds from huge chemical libraries toward proven target proteins. Ligand-based virtual screening techniques employing two-dimensional fingerprint similarities, exemplified by ECFP4-based methods utilized in

SwissSimilarity, facilitate the effective exploration of synthesizable chemical space surrounding a novel scaffold. Complementary *in silico* ADMET profiling and structure activity relationship study (SAR) helps figure out the pharmacokinetic and toxicological problems with a candidate early on along with its structural correlation with activity, which helps optimize its structure before expensive experimental validation [16–21].

In spite of these Improvements no approved oral small molecule GLP-1R agonist is designed upon an indoloquinoxaline-based tetracyclic structure, and the structural elements of binding in this chemical class are still unexamined. In this study, we present the rational design and *in silico* assessment of ThiaGlip-1, a novel small-molecule GLP-1R agonist candidate featuring an unprecedented indolo[1,2-b]quinoxaline tetracyclic core that is structurally distinct from all previously characterized GLP-1R agonist scaffolds. We did molecular docking validation, virtual screening of 380 Enamine_Tang library compounds, ADMET profiling, and SAR analysis to find lead candidates and figure out what structural factors affect GLP-1R binding affinity in this new chemical series.

MATERIALS AND METHODS

ThiaGlip-1 Hybrid Scaffold Design

ThiaGlip-1 is a small-molecule GLP-1R agonist candidate that was designed around a new indolo[1,2-b]quinoxaline tetracyclic nucleus. The scaffold was rationally constructed by integrating structural and pharmacophoric features from two well-characterised GLP-1R small-molecule agonist series: the fluoropyrimidine-based agonist Danuglipron (PF-06882961), which established the importance of a carboxylic acid anchor for salt-bridge formation with Arg190 (TM2) [10,13], and the indoloquinoxaline-based agonist PK2, which demonstrated the suitability of fused polycyclic aromatic systems for engagement with the tryptophan-rich extracellular domain of GLP-1R[12]. The indolo[1,2- b]quinoxaline core of ThiaGlip-1 represents a novel regioisomeric variant of the PK2 scaffold, with C8-thiophene and triazole-linked carboxyphenyl extensions introduced to optimize orthosteric pocket occupancy and pharmacokinetic profile, in addition to the distinct locations of ring fusion (N1–C2 for ThiaGlip-1 versus C2–C3 for PK2) with a Tanimoto similarity of only 0.41 calculated using RDKit 2023.09, confirming its novelty. The structure has four pharmacophoric parts that work together to target the main contact areas of the human GLP-1R orthosteric pocket. These contact areas are the salt-bridge residue Arg190 (TM2), the hydrophobic lid residue Trp33 (ECD), and the aromatic tryptophan cluster of the extracellular domain (Trp39, Trp42) [9,22,23]. The four pharmacophoric elements were: an indolo[1,2-b]quinoxaline tetracyclic core (benzene–pyrrole–pyrazine–benzene), that provides a solid plane scaffold for deep infiltration into the transmembrane pocket and van der Waals interactions with hydrophobic residues; a fully N-substituted 1,2,3-triazole ring as a biologically stable bioisosteric linker; a thiophene ring positioned at C8 of the quinoxaline-fused benzene, working as a π–π stacking for Trp33 and the ECD tryptophan cluster; and a para-carboxyphenyl group as an acidic anchor that provides a salt bridge with TM2, straightly resembling the Glu9 interaction of original GLP-1 and mimicking the potency-boosting strategy of Danuglipron [10]. Figure (1) presented ThiaGlip-1 molecular structure.

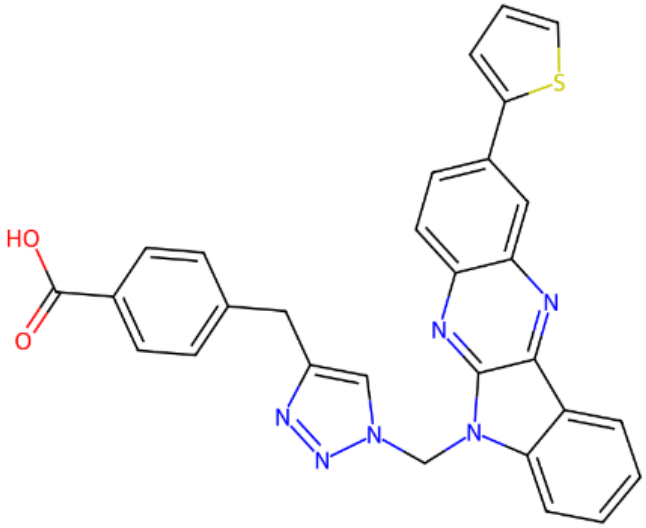


Figure (1): The 2 dimensional molecular structure of ThiaGlip-1. Molecular formula: $C_{29}H_{20}N_6O_2S$, Molecular weight: 516.59 Da, Log P 5.85, and TPSA 98.72 Å². SMILES: OC(=O)c1ccc(Cc2cn(CN3c4ccccc4c5nc6cc(c7cccs7)ccc6nc35)nn2)cc1. In ChI Key: FLHMZNDBHMEFLD-UHFFFAOYSA-N.

Protein Target Preparation

We acquired the three-dimensional structure of the human GLP-1R from the RCSB Protein Data Bank (PDB ID: 7LCJ; cryo-EM resolution 3.0 Å). It reveals the fully active receptor shape that was captured with the small-molecule agonist Danuglipron, the heterotrimeric Gs protein, and stabilizing nanobody 35 (Nb35). We only kept the GLP-1R polypeptide chain (chain R; 390 residues, range 28–423) for docking. The Gs protein and Nb35 are only there to stabilize the receptor complex for cryo-EM imaging and don't affect the small-molecule binding pocket. This is in line with what has been established about how to dock small molecules with class B GPCRs. All of the HETATM records were removed to create a receptor structure that could be used for docking. These records included the ligand that was co-crystallized, cholesterol hemisuccinate [3,11] , in addition to the crystallographic water molecules, which were removed before docking according to standard molecules docking protocols by AutoDock Vina which is used to dock this class B GPCRs transmembrane sites of binding [24,25].

The extracted chain missing six residues at positions 129–134. These residues occur at a flexible extracellular stalk loop that connected the transmembrane domain to the N-terminal ectodomain. As a result, Cryo-EM electron density was not strong enough in this very mobile area, which is why they did not exist there. The missing piece is not very important because this loop is too far away from the orthosteric binding pocket [3,11]. To complete protein preparation, we added polar hydrogen atoms and used Open Babel 3.1.0 to figure out the Gasteiger partial charges at a pH of 7.4, which is normal for the body. The receptor that was created was saved in PDBQT format to be docked using AutoDock Vina 1.2.3 [25].

Molecular Docking and Protocol Validation

All calculations for molecular docking were done via AutoDock Vina 1.2.3 with the default Vina scoring function, an exhaustiveness of 8, and a maximum of 9 binding poses per ligand. The seven important orthosteric residues: Trp33, Trp39, Trp42, Tyr152, Arg190, Lys197, and Gln234 were covered by the cubic grid box with dimensions of 25 × 25 × 25 Å³ (x = 123.07, y = 155.50, z = 113.55 Å). It was verified that all seven residues were contained within the grid box. In other words, the deep transmembrane orthosteric pocket, important for small-molecule GLP-1R agonism, formed by helices TM1, TM2, TM3, and TM7, which interact with the salt-bridge contact with Arg190 and the π–π stacking interactions with Trp33 and Trp39/Trp42, was part of this search space [9].

All ligands, including the validation compound, ThiaGlip-1, and the 400-compound virtual screening library, were prepared using a uniform protocol: three-dimensional conformers were generated from canonical SMILES strings using RDKit 2023.09, and heavy-atom coordinates were written to PDBQT format with Gasteiger partial

charges. The prepared receptor file and grid box parameters were applied uniformly across all docking runs.

Before ThiaGlip-1 and the virtual screening library molecular docking, the docking protocol was validated by re-docking Danuglipron (PF-06882961), the reference agonist, into the prepared GLP-1R structure (PDB ID: 7LCJ). Danuglipron was chosen as the validation compound due to its availability as the co-crystallized small-molecule agonist in the 7LCJ structure, well characterized binding interactions with GLP-1R are at atomic resolution, and independently calculated docking affinity which had been reported across multiple computational studies. Its SMILES string was retrieved from PubChem and processed via the same preparation pipeline applied to all other ligands [10].

Molecular Docking of ThiaGlip-1

ThiaGlip-1 was docked versus the previously prepared GLP-1R structure utilizing the validated protocol described in Section 2.3. RDKit 2023.09 was utilized to generate the three-dimensional conformation from canonical SMILES string, and AutoDock Vina 1.2.3 was used to perform docking, with exhaustiveness = 8, a maximum of 9 poses, and the same grid box dimensions used in the validation step.

Virtual Library Generation

SwissSimilarity (www.swisssimilarity.ch), a web-based ligand-based virtual screening platform, was utilized for virtual compound library generation [19]. ThiaGlip-1 was introduced as the query molecule in SMILES format, and similarity searching was performed towards the Enamine_Tang, a compound library compiled from Enamine Ltd. in collaboration with Tang et al., using the ECFP4 (Extended Connectivity Fingerprint, diameter 4) two-dimensional fingerprint method. The search was restricted to synthesizable compounds only to ensure that all acquired candidates are readily accessible for potential experimental validation. A total of 400 structurally similar compounds were retrieved and retained for subsequent molecular docking against the GLP-1R. The virtual library is somewhat small because of intentional utilization of a ligand-dependent similarity method of search instead of a full screening. Additionally, to guarantee experimental availability of all recognized candidates the search was limited to synthesizable compounds from the Enamine_Tang library. This strategy targets structural similarity to ThiaGlip-1 rather than chemical diversity.

Molecular Docking of the Virtual Library

The same AutoDock Vina 1.2.3 protocol from Section 2.3 was used to dock the 400 compounds from SwissSimilarity towards the prepared GLP-1R structure (PDB ID: 7LCJ). Utilizing RDKit, we made three-dimensional conformers from the SMILES strings of each compound. Then, we changed the format to PDBQT and added Gasteiger partial charges. Finally, we docked them with exhaustiveness = 8 and a maximum of 9 binding poses per ligand. We excluded the compounds that failed to be converted into three-dimensional conformers. After that, we arranged the docking scores from most to least negative and put the compounds into four groups, based on how strongly they bind to the receptor's active site, as follow: Excellent (≤ −9.0 kcal/mol), Good (−9.0 to −8.0 kcal/mol), Moderate (−8.0 to −7.0 kcal/mol), and Weak (> −7.0 kcal/mol).

ADMET Profiling

A rule-based computational pipeline in RDKit was utilized to do a full ADMET profile analysis, which include absorption, distribution, metabolism, excretion, and toxicity, using known physicochemical cutoffs based on Lipinski's Rule of Five, Veber's criteria, and published toxicological cutoffs .This was chosen to allow high-performance batch screening of all 380 library compounds in a reproducible and automated manner, as online platforms such as SwissADME and pkCSM do not support automated batch computation of compound libraries of this size. Although rule-based ADMET estimation is regarded as an approximation, the thresholds used are well confirmed in the literature and are adequate for early-stage lead ranking before experimental verification [26,27]. This analysis was done for ThiaGlip-1 along with the complete library compound candidates that successfully docked. Physicochemical descriptors for each compound were calculated, such as molecular weight (MW), lipophilicity (LogP), topological polar surface area (TPSA), hydrogen bond donor and acceptor counts (HBD, HBA), and the number of rotatable bonds

(RotBonds). By using an established physicochemical threshold, ADMET endpoints were predicted. Blood–brain barrier (BBB) penetration was predicted as positive if MW < 400 Da, LogP between 1 and 3, TPSA < 90 Å², and HBD ≤ 3. On the other hand, human intestinal absorption (HIA) was classified as High if MW < 500 Da, LogP between 1 and 5, TPSA < 140 Å², and RotBonds < 10. Concerning hERG cardiac liability, it was computationally screened at the early stage using a well-defined LogP threshold (LogP > 3.5), where lipophilicity is considered as a primary physico-chemical determinant for hERG channel interaction [28]; hepatotoxicity risk was assigned if LogP > 4. Additionally, skin sensitization risk was also evaluated on the basis of combined LogP (LogP > 3) and molecular weight (MW > 400 Da) thresholds, representing the physicochemical specifications for dermal penetration and protein haptenation, along with confirmed descriptors in existing skin sensitization models for prediction [29]. These rule-based predictions are straightforward substitutions for more rigorous structure-based tools but are in line with accepted early-stage computational toxicology guidelines and adequate for early lead classification prior to experimental validation. Without any known structural alerts, AMES mutagenicity was set to Negative by default for all screened compounds due to the lack of any known mutagenic structural alerts especially nitroaromatic groups, aromatic amines, epoxides and alkylating agents in the investigated compound structures [30]. This is additionally boosted by published screened data indicating that approximately 77% of Enamine library molecules are free from recognized toxicological structural hazards as checked by the ToxAlerts platform, indicating a generally favorable safety profile for this compound class [31]. This assignment is considered acceptable as a first-pass estimation, and a detailed AMES prediction employing validated tools such as admetSAR or pkCSM should be carried out for experimental follow-up of the lead candidates identified. By using Veber's criteria (RotBonds ≤ 10, TPSA ≤ 140 Å²) as well as Lipinski's Rule of Five (MW ≤ 500 Da, LogP ≤ 5, HBD ≤ 5, HBA ≤ 10) drug-likeness and oral bioavailability were evaluated. Based on the total number of toxicity flags and drug-likeness violations, an overall drug score was given on a scale from 0.1 to 1.0. Higher scores mean better profiles, to find the best lead candidates for further development [20].

SAR Analysis

SAR analysis was conducted to find the physicochemical descriptors that were most strongly linked to docking score across the compounds virtual library. For each compound, nine molecular descriptors were checked which include: MW, LogP, HBD, HBA, TPSA, RotBonds, RingCount (number of rings), ArRings (number of aromatic rings), and HeavyAtoms (number of heavy atoms). SciPy was utilized to calculate Pearson correlation coefficients (r) between each descriptor and the AutoDock Vina docking score. To enhance the univariate evaluation, and to consider a possible inter-descriptors collinearity, a multiple linear regression (MLR) model was established based on the nine standardized descriptors as independent variables and the score for docking as dependent variable. This allows to assess the overall explanatory capacity of the descriptor set, and to recognize collinear relationships among predictors, with a statistical significance checked at $\alpha = 0.05$.

The descriptors were grouped by how strong the correlation was, with higher number means better correlation, as follow: $|r| \geq 0.7$ = Very Strong, $0.5 \leq |r| < 0.7$ = Strong, $0.3 \leq |r| < 0.5$ = Moderate, and $|r| < 0.3$ = Weak. We also looked at Lipinski Rule of Five compliance as a categorical variable to see how it affected the distribution of binding affinities. We did this by using overlapping histograms and box plots to compare the score distributions of compliant and non-compliant subsets [32].

RESULTS AND DISCUSSION

Docking Protocol Validation and Molecular Docking of ThiaGlip-1

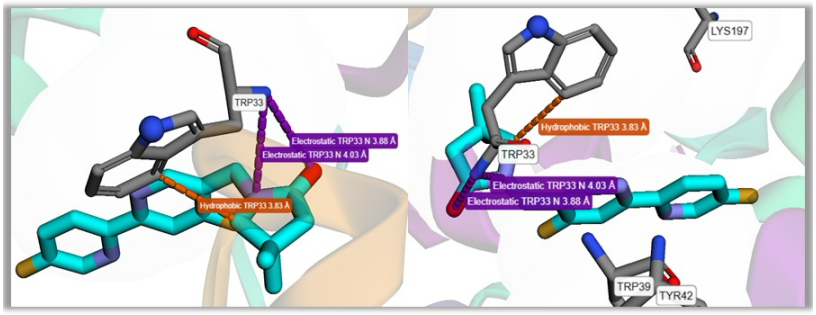
To confirm the validity of the molecular docking technique before performing molecular docking for ThiaGlip-1 and the virtual library, the well-known GLP-1R small-molecule agonist Danuglipron was re-docked versus the active-state GLP-1R structure's orthosteric binding site (PDB ID: 7LCJ) as a positive control. Danuglipron had a best docking score of −9.763 kcal/mol across nine predicted poses, with scores ranging from −9.763 to −7.388 kcal/mol. This assures that binding to the transmembrane orthosteric pocket is consistent and stable in all of the poses that were produced. The intimate match between this value and the literature-reported binding affinity, which is about −11 kcal/mol for Danuglipron at the same receptor structure, confirms that the docking protocol and grid box settings are reliable for future screening [33]. The small difference of 0.74 kcal/mol is within the acceptable range of 2–4 kcal/mol for scoring variation in comparative docking studies [26,27]. Table (1) illustrated all 9 docking scores for Danuglipron. No formal RMSD calculation was carried out, as the computational conformer was obtained de novo from SMILES, not directly from crystallographic coordinates, and atom-by-atom superposition with the crystallographic pose is not strictly correct, since the de novo conformer has its own energy-minimised internal geometry, which is fundamentally different from the crystallographic coordinates, as noted in the docking papers [34]. As an alternative spatial validation metric, the centre-of-mass displacement of 1.778 Å between the re-docked pose and the crystallographic site of binding was calculated, confirming accurate binding site localization [35].

After the protocol was validated, the new hybrid scaffold ThiaGlip-1 was docked toward the same prepared GLP-1R structure under the same conditions. ThiaGlip-1 had the best docking score of −9.222 kcal/mol throughout three different binding poses, with scores of −9.222, −7.879, and −6.938 kcal/mol and these three poses showed geometrically distinct binding modes within the orthosteric pocket as AutoDock Vina automatically clusters and removes binding poses that are very close to each other by an internal RMSD threshold, thus leaving just geometrically different poses. Hence, only three different binding modes were found in the orthosteric search space for ThiaGlip-1, instead of the maximum nine. The difference of 0.541 kcal/mol in relation to Danuglipron is within the acceptable range of scoring variation, which means that ThiaGlip-1 is a compound with a predicted binding affinity that is similar to that of the clinically tested reference agonist. This supports the validity of the rational hybrid design strategy [36,37]. Figure (2) shows Danuglipron and ThiaGlip-1 interactions inside the GLP-1R binding pocket.

Table (1): The docking scores for Danuglipron.

Pose	Score (kcal/mol)
1	−9.763
2	−9.623
3	−9.187
4	−8.354
5	−8.331
6	−8.186
7	−8.043
8	−8.009
9	−7.388

(A) Danuglipron interactions inside the GLP-1R binding pocket



(B) ThiaGlip-1 interactions inside the GLP-1R binding pocket

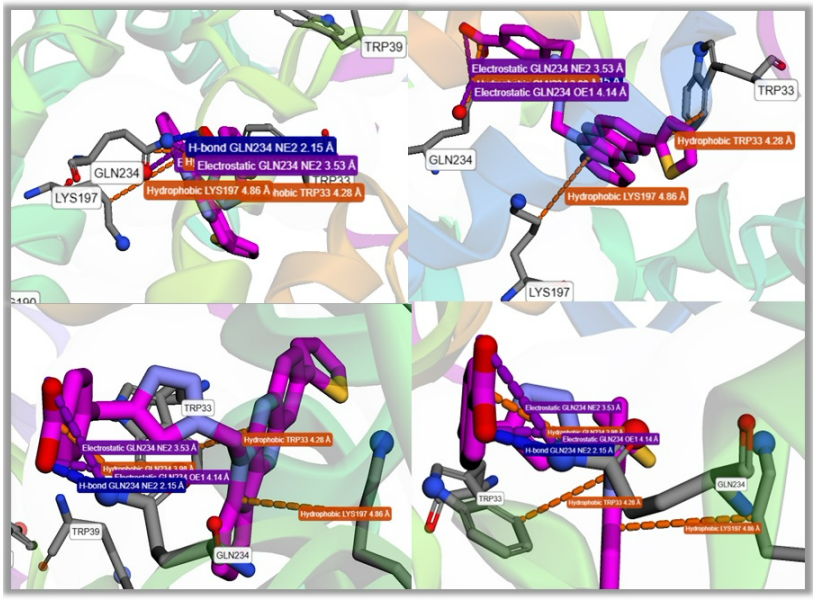


Figure (2): 3-Dimensional Ligand-interaction diagrams illustrating anticipated binding poses of Danuglipron (A) and ThiaGlip-1 (B) in the GLP-1R orthosteric pocket (PDB: 7LCJ). The main interactions observed are hydrophobic interaction, electrostatic interaction, and H bond interaction. Docking scores: Danuglipron: −9.763 kcal/mol, ThiaGlip-1: −9.222 kcal/mol.

Virtual Screening of the Library of 400 Compounds

Virtual library of 400 structurally similar compounds was retrieved from the Enamine_Tang library via SwissSimilarity using ECFP4 fingerprint similarity with ThiaGlip-1 as the query molecule. After applying the docking protocol, 380 compounds were successfully docked toward GLP-1R (PDB ID: 7LCJ) after effectively generating a three-dimensional conformer. The remainder of 20 compounds were ignored because the conformer generation failed mostly due to significantly tight ring systems or unresolvable stereochemical arrangements and were not taken into account during a docking investigation. However, the inability to generate conformers has no effect on the pharmacophore similarity to ThiaGlip-1 and, therefore, such an exclusion will not cause a systematic bias to the screening outcomes. The binding profile was very good, with 294 candidates considered as excellent binders, 69 candidates were good binders, 14 candidates were moderate binders, and there were only three weak binders among the candidates. Docking ratings ranged between −12.931 and −6.189 kcal/mol, the average score for the library was −9.756 kcal/mol, which is superior to Danuglipron and ThiaGlip-1 with affinities of −9.763 kcal/mol and −9.222 kcal/mol, respectively. PV-004794919713, the compound with the best score, achieved a score of −12.931 kcal/mol. This was significantly greater than the scores for the reference, Danuglipron. This indicates that the choice of Enamine_Tang library was well-suited as this library has numerous compounds that are structurally similar and are likely to bind strongly to GLP-1R. Table (2) illustrated the top 10 compounds with regard to docking scores.

Table (2): Top 10 compounds according to docking scores.

Rank	Compound ID	Score (kcal/mol)
1	PV-004794919713	-12.931
2	PV-005502782345	-12.876
3	Z360876158	-12.581
4	Z4594432747	-12.429
5	Z5017178759	-12.324
6	Z3838693143	-12.275
7	PV-002918833325	-12.071
8	PV-004003938144	-11.959
9	PV-004046754233	-11.959
10	PV-002853013918	-11.919

ADMET Profiling

ADMET Profile of ThiaGlip-1

A full *in silico* ADMET profile of ThiaGlip-1 confirmed that it had a mixed pharmacokinetic and toxicological profile. Even the rule-based pipeline classified human intestinal absorption (HIA) as high based on TPSA and RotBonds, the compound fails to meet Lipinski's Rule of Five because it has two borderline violations (MW = 516.59 Da and LogP = 5.85). However, it satisfies Veber's criteria (RotBonds = 6, TPSA = 98.72 Å²), which suggests that oral bioavailability, even though it is difficult, may be possible. AMES mutagenicity was negative, which means that the drug is not likely to pose a direct mutagenic risk. Unfortunately, ThiaGlip-1 has three toxicity flags mainly because it has a high LogP (5.85) and MW (516.59 Da). These flags are for hERG cardiac liability, hepatotoxicity risk, and skin sensitization risk. It was predicted that BBB penetration for ThiaGlip-1 is negative. The overall drug score of 0.6 indicates that ThiaGlip-1 needs structural optimization, especially lowering LogP, to improve its pharmacological profile. ThiaGlip-1 was maintained as the design scaffold despite two violations of Lipinski's rule and three predicted toxicity flags, based on its expected binding affinity of −9.222 kcal/mol which was comparable to the clinically approved reference agonist Danuglipron (−9.763 kcal/mol). In rationalized scaffold-based drug development, the initial scaffold does not need to have an optimal pharmacokinetic profile but should be a structural scaffold that can be used to benefit from binding interactions and physicochemical liabilities by systematic library production and lead optimization. Thus, a virtual library of 380 structurally related compounds was created to discover analogues that maintain the optimal binding properties of ThiaGlip-1 but improve its ADMET profile.

ADMET Profiling of the 380-Compound Library

ADMET profiling of the 380-compound library showed a markedly superior pharmacokinetic and safety profile relative to ThiaGlip-1, as clarified in Table (3) and Figure (3). All 380 compounds achieved High HIA and satisfying both Lipinski and Veber drug-likeness criteria along with Negative AMES mutagenicity, with 378 compounds (99.5%) predicted as hepatotoxicity-safe. BBB penetration was predicted for 336 compounds (88.4%), and hERG safety was confirmed for 271 compounds (71.3%). A total of 270 compounds (71.1%) carried zero toxicity flags and reached a mean drug score of 1.00, representing the highest-priority candidates for lead optimization. The three top-ranked compounds by combined docking score and ADMET profile were Z4594432747 (−12.429 kcal/mol), PV-002918833325 (−12.071 kcal/mol), and PV-004003938144 (−11.959 kcal/mol), all carrying zero toxicity flags and passing all drug-likeness criteria. Top 10 library compounds detailed ADMET profile is listed in Table (4).

Table (3): ADMET profiling of the 380-compound library.

Parameter	Value	Implication
HIA High	380 (100.0%)	Excellent absorption
BBB Yes	336 (88.4%)	CNS penetration possible
hERG Safe	271 (71.3%)	Good cardiac safety
AMES Negative	380 (100.0%)	No mutagenicity
Hepatotox Safe	378 (99.5%)	Excellent liver safety
Lipinski Pass	380 (100.0%)	Excellent drug-likeness
Veber Pass	380 (100.0%)	Oral bioavailability favorable
Zero tox flags	270 (71.1%)	Top priority candidates
Mean Drug Score	1.00	Excellent overall profile (based on Lipinski and Veber drug-likeness criteria)
Mean Docking Score	−9.756 kcal/mol	Strong GLP-1R binding

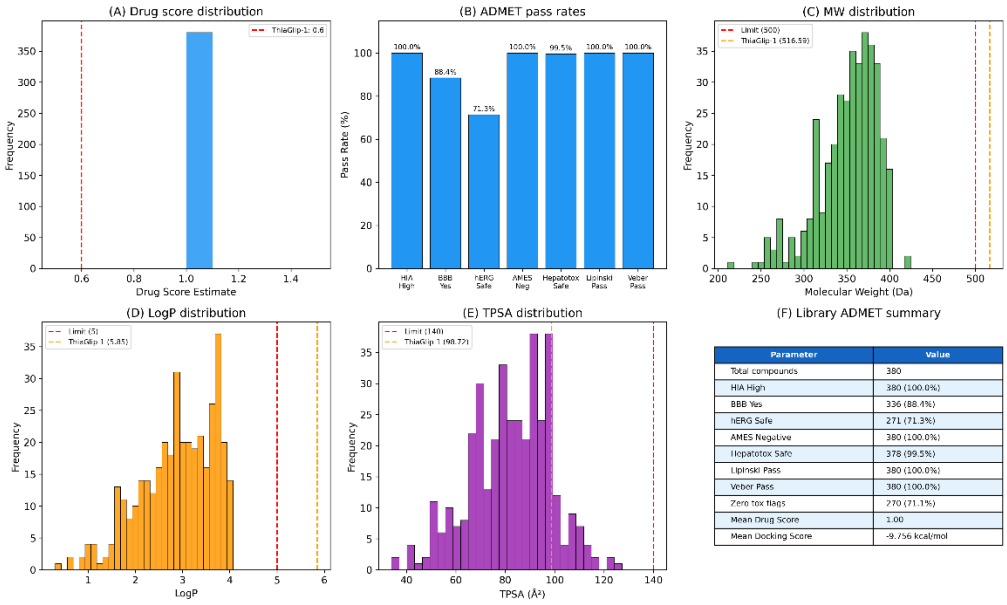


Figure (3): Full *in silico* ADMET profile of the 380-compound virtual library the bar charts represent the percentage of compounds satisfying each pharmacokinetic and safety parameter: HIA (100%), BBB penetration (88.4%), hERG safety (71.3%), AMES negativity (100%), hepatotoxicity safety (99.5%), Lipinski compliance (100%), and Veber compliance (100%). Top-priority lead candidates identified as compounds with zero toxicity flags (71.1%).

Table (4): Comprehensive ADMET profile for top 10 library compounds.

#	Compound ID	Score (kcal/mol)	Drug score	Tox flags	hERG	Hepatotox	Skin sens.	Lipinski
1	PV-004794919713	−12.931	1.0	1	Risk	Safe	Safe	Pass
2	PV-005502782345	−12.876	1.0	1	Risk	Safe	Safe	Pass
3	Z360876158	−12.581	1.0	1	Risk	Safe	Safe	Pass
4	Z4594432747	−12.429	1.0	0	Safe	Safe	Safe	Pass
5	Z5017178759	−12.324	1.0	1	Risk	Safe	Safe	Pass
6	Z3838693143	−12.275	1.0	1	Risk	Safe	Safe	Pass
7	PV-002918833325	−12.071	1.0	0	Safe	Safe	Safe	Pass
8	PV-004003938144	−11.959	1.0	0	Safe	Safe	Safe	Pass
9	PV-004046754233	−11.959	1.0	0	Safe	Safe	Safe	Pass
10	PV-002853013918	−11.919	1.0	0	Safe	Safe	Safe	Pass

SAR Analysis

SAR analysis was done to identify the physicochemical descriptors most strongly correlated with binding affinity to GLP-1R across the 380-compound library. Pearson correlation coefficients between nine molecular descriptors and AutoDock Vina docking scores were examined. LogP, ArRings, and HeavyAtoms, with (r) values of −0.424, −0.419, and −0.417, respectively, considered as the strongest moderate correlate of binding affinity, as they show moderate but statistically significant relationships with $p < 0.001$ in all cases. In addition, the moderate degree of these correlations is in line with the relatively compact physicochemical range of the Enamine_Tang library (MW 211–424 Da, LogP 0.31–4.07), which consequently minimizes variation in descriptor values. The relationship with these three molecular descriptors suggesting that higher lipophilicity and greater aromatic surface area linked with stronger predicted binding affinity. This finding is consistent with the GLP-1R transmembrane orthosteric pocket hydrophobic character, which is formed by helices TM1, TM2, TM3, and TM7 and lined with aromatic residues including Trp33, Trp39, Trp42, and Tyr152, all of which are well-positioned to engage in π–π stacking and van der Waals interactions with lipophilic aromatic systems 9. Ring count also indicated a moderate negative correlation (r = −0.345), that further supporting the importance of rigid polycyclic scaffolds for productive binding within this cavity.

On the other hand, HBA showed a moderate positive correlation (r = +0.343), indicating that compounds with greater polar acceptor groups tended toward weaker binding, consistent with the hydrophobic nature of the pocket. TPSA (r = +0.002) and HBD (r = −0.018) reveal negligible correlations, confirming that total polar surface area and hydrogen bond donor capacity were not important predictors of GLP-1R binding affinity. It is important to note that although HBA and TPSA usually correlate with each other, in this library the hydrogen bond acceptor groups were not directly related with increasing the total polar surface area of the compound, this is due to intramolecular shielding of polar groups. Based on that, HBA may reflect the size dependent effects rather than the polarity alone, as larger compounds tend to have more hydrogen bond acceptor groups. All 380 compounds of the virtual library passed Lipinski's Rule of Five, with 100% compliance, confirming excellent oral drug-likeness across the entire screened set. Scatter plots of all nine descriptors against docking scores to show how the descriptors are related to each other are clarified in Figure (4). The MLR model that utilizes all nine

descriptors achieved $R^2 = 0.442$ (adjusted $R^2 = 0.428$), suggesting that the entire set of physicochemical descriptors determines about 44% of the variation in affinity for binding. This moderate R^2 fits in with the well-known fact that experimental docking scores are predominantly affected by three-dimensional protein–ligand complementarity characteristics not only the bulk physicochemical parameters [36]. When inspecting the defined MLR coefficients, HeavyAtoms ($\beta = -1.14$) and MW ($\beta = +0.82$) displayed opposite signs, which was due to the significant inter-descriptor collinearity (Pearson $r = 0.93$), a well-known restriction of MLR when highly correlated predictors are present [38]. In such cases individual regression coefficients are unstable and not reliably interpretable, and univariate Pearson correlations offer a more solid representation of individual descriptor-affinity associations [39]. Collectively, the SAR analysis supports lipophilicity and aromatic ring content as the main physicochemical variables that determine GLP-1R affinity for binding in the screened library, in agreement with previously reported research involving small-molecule GPCR agonists that target hydrophobic transmembrane pockets [40].

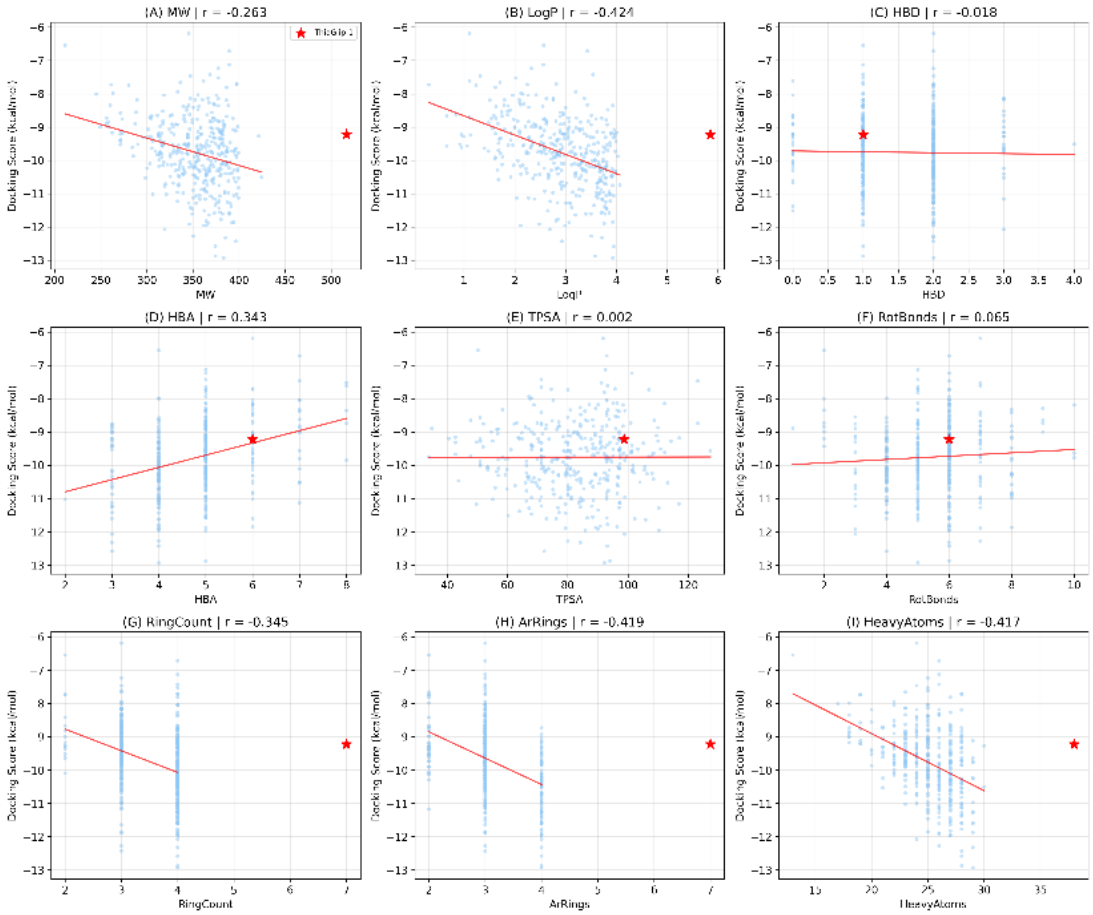


Figure (4): SAR evaluation of the virtual library of 380 compounds Scatter plots display Pearson correlation coefficients among nine physicochemical descriptors (MW, LogP, HBD, HBA, TPSA, RotBonds, RingCount, ArRings, HeavyAtoms) and AutoDock Vina docking scores. The most significant moderate correlations were found for LogP ($r = -0.424$), ArRings ($r = -0.419$) and HeavyAtoms ($r = -0.417$), suggesting that lipophilicity and aromatic ring content are the main physicochemical indicators of GLP-1R binding affinity in this library.

CONCLUSION

This study introduces the rational *in silico* designing and computational assessment of ThiaGlip-1, an innovative small-molecule GLP-1R agonist based on a previously unreported indolo[1,2-b]quinoxaline tetracyclic core. Molecular docking versus active human GLP-1R (PDB ID: 7LCJ) showed that ThiaGlip-1 had the best binding affinity of −9.222 kcal/mol, which is close to the reference agonist Danuglipron (−9.763 kcal/mol). This indicates that the four-pharmacophore hybrid design approach is effective. Virtual screening of 380 Enamine_Tang compounds revealed 294 candidates (77.4%) with excellent binding affinity. The best compound, PV-004794919713, possessed a binding affinity of −12.931 kcal/mol. Concerning SAR analysis, LogP, ArRings, and HeavyAtoms were identified to be the main contributors of GLP-1R binding affinity. This is in line with the fact that the transmembrane orthosteric pocket of GLP-1R is hydrophobic. ADMET profiling revealed that a total of 270 library compounds (71.1%) have no toxicity flags and a mean drug score of 1.00. The three best candidates, Z4594432747, PV-002918833325, and PV-004003938144, emerged to be the best leads as they had excellent docking scores (around −12.0 kcal/mol), full Lipinski and Veber compliance, and no predicted toxicity. Ultimately, the rational design approach illustrated here, which is based on established pharmacophoric evidence and an integrated computational method, creates a new and distinctive structural scaffold for further development as an orally active GLP-1R agonist for treating obesity and type 2 diabetes. To achieve this, future work should focus on performing molecular dynamics simulations (minimum 100 ns) of the best lead candidates to evaluate the stability and dynamic behavior of the estimated binding complexes over time, beyond the static docking findings presented here. In addition, all results are preliminary and need experimental validation such as binding analysis, cellular GLP-1R stimulation tests, and *in vivo* pharmacokinetic evaluation before any clinical conclusions can be reached.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

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