RESEARCH PAPER

In-Silico Design and Evaluation of Novel Pyranopyrimidine Analogues as SGLT2 Inhibitors: A Comparative Study with Sotagliflozin

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ABSTRACT

Background

The Sodium glucose co-transporter-2 (SGLT2) is responsible for the transport of 90% glucose in the kidneys. The inhibition of this transporter ensures that sugar is removed through urine, hence lowering the levels of sugar in the blood without increasing insulin levels.

Objective

Create a library of analogues with different functional groups such as alkyl, halogen, amino, and nitro. Lipinski's Rule of Five, Ghose, Veber, Egan, and Muegge filters will be applied. ADME Prediction: Predict Absorption, Distribution, Metabolism, and Excretion of drugs within the body using Generalized Absorption, Permeability of Blood-Brain Barrier, and Inhibition of CYP450 Enzymes. Toxicity Risk Assessment: Use modeling techniques for risk assessment regarding hepatotoxicity, neurotoxicity, nephrotoxicity, cardiotoxicity, and respiratory toxicity.

Methods

Ligand Preparation and Library Design: We have developed a library of 34 analogues based on a modified Sotagliflozin template. We have replaced the core with different alkyl, halogen, and polar functional groups such as hydroxyl, amino, nitro, and ester. We have processed the SGLT2 template after removing water molecules and co-crystallized ligands.

Results

We have conducted a series of docking experiments for all analogues and SGLT2 with two crystal structures: 7VSI and 8HG7. We have validated our experiment with Sotagliflozin, where binding energy is -9.0 kcal/mol for 7VSI and -8.0 kcal/mol for 8HG7. Top Performer: A15: The compound A15 with dichloro functional groups was found to have the highest binding affinity with a binding energy value of -9.3 kcal/mol for 8HG7.

Conclusion

It is evident from this comprehensive analysis that the pyranopyrimidine nucleus acts as a bioisostere for developing SGLT2 inhibitors. We were successful in developing some binding affinities better than Sotagliflozin itself (A14, A15, and A29). A15, with a binding energy value of -9.3 kcal/mol.

Keywords: Diabetes mellitus, sotagliflozin, pyranopyrimidine, SGLT2, SWISSADME, PROTOX-III, Docking

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1.Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion, action, or both [1]. The global burden of diabetes has risen alarmingly over the past several decades, which has created challenges in the treatment of the disease due to the associated micro- and macrovascular complications, including nephropathy, neuropathy, retinopathy, cardiovascular diseases, and compromised quality of life [2,3]. Despite the availability of a number of drugs belonging to different pharmacological classes, the maintenance of optimal glucose levels in the body continues to pose a challenge in the treatment of the disease, thus

necessitating the search for new, effective, and better therapeutic agents [4].

Among the new developments in the treatment of the disease, SGLT inhibitors represent an important class of oral hypoglycemic agents, which reduce blood glucose levels by inhibiting glucose reabsorption in the kidneys [5]. Sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, has been shown to reduce glucose levels in the body, which is a unique action compared to other SGLT inhibitors, as it acts on two transporters, one in the intestine and the other in the kidneys, which are responsible for glucose absorption in the body [6]. This dual action not only provides better control of glucose levels but also has beneficial effects on body weight and cardiovascular parameters [7]. Despite the beneficial effects of the compound, the clinical use of the drug has been limited due to certain limitations, including gastrointestinal side effects, the risk of hypoglycemia under certain conditions, and limitations in the assessment of the long-term effects of the compound, which are undesirable [8,9].

The modification of existing drugs, which are in use, has been an approach in medicinal chemistry, which has been widely accepted as a means of enhancing the pharmacological effects of the compounds, while at the same time reducing the undesirable effects [10]. The development of new analogues of the compound, which has been shown to possess a unique mechanism of action in the treatment of the disease, offers an opportunity to improve the interaction of the compound with the SGLT transporters, while at the same time eliminating the undesirable effects, which are associated with the clinical use of the compound [11,12].

In this regard, the present research is aimed at designing novel analogues of Sotagliflozin as potential antidiabetic agents. Through this approach, this study may contribute to the discovery and development of new and improved SGLT inhibitors that may prove to be more efficacious and safer for the treatment of diabetes mellitus [13].

Sodium-glucose cotransporter 2 (SGLT2) is primarily expressed in the S1 segment of the renal proximal convoluted tubule and is responsible for the reabsorption of nearly 90% of the glucose present in the glomerular filtrate. The inhibition of this transporter results in a decrease in the renal threshold for glucose, causing an increased loss of glucose in the urine, and subsequently lowering the plasma glucose levels through an insulin-independent mechanism. This is a unique action compared to other antidiabetic agents and is responsible for the use of these agents for the treatment of diabetes at all stages, including those with insulin resistance or β-cell dysfunction. Apart from lowering blood glucose levels, these agents have shown significant benefits, including a slight reduction in body weight, lowering of systolic blood pressure, and significant cardioprotective and renoprotective effects, including a reduction in hospitalizations for heart failure and a decrease in the progression of chronic kidney disease. Adverse effects, such as genital mycotic infections and volume depletion, and, rarely, euglycemic diabetic ketoacidosis, are also class-related side effects that need to be addressed through improved target selectivity and pharmacokinetic properties. Sotagliflozin, a dual SGLT1/2 inhibitor, is an extension of this therapeutic approach, also restricting intestinal glucose uptake, and hence improving postprandial glucose excursions, although at the cost of increased gastrointestinal side effects [21,22]. These limitations offer a strong rationale for the rational design of novel sotagliflozin analogs with better SGLT2 selectivity, metabolic stability, and an optimized balance of efficacy and safety.

We have also attempted to optimize the pyranopyrimidine moiety. The pyranopyrimidines contain the fusion of pyran and pyrimidin rings. These types of rings are preferred in drug design due to their stability and ability to act as hydrogen bond acceptors. We are expecting that the incorporation of these types of rings into the gliflozins will result in changes in pharmacology and pharmacokinetics.

'Gliflozins' have brought about an enormous shift in the treatment of diabetes. Canagliflozin, Dapagliflozin, and Empagliflozin have established C-glycosides as an unrivaled benchmark. Safety issues, Urinary Tract Infections, and Diabetic Ketoacidosis have also appeared on the scene.

Recent studies have shown that heterocyclic fusion rings, pyranopyrimidines, have shown varying biologic activities, ranging from antimicrobial to anticancer properties. Their use as SGLT2 inhibitors is an emerging concept. To achieve this, it is imperative that computational research is carried out. By so doing, it would be feasible to screen a vast amount of data and filter out compounds with unfavorable ADMET properties prior to synthesizing the compounds. Prediction of physicochemical properties and binding domains was done using SwissADME and Auto-Dock Vina, respectively.

2.METHODOLOGY

2.1Ligand Preparation and Library Design-

We have make a library of 34 pyranopyrimidines based on a modified Sotagliflozin scaffold. We replaced the central core with alkyl moieties (methyl, ethyl, and propyl), halogens (fluorine, chlorine, and bromine), and various polar functionalities (hydroxyl, amino, nitro, and ester)[26]. We converted these 2D molecules into 3D energy-minimized conformers[25].

S.NO	Molecule ID	SMILES (Chemical Structure Code)	Formula	MW (g/mol)
1	Molecule 1	Cc1ncnc2c1CCCO2	C8H10N2O	150.18
2	Molecule 2	Cc1nc2OCCCc2c(n1)C	C9H12N2O	164.2
3	Molecule 3	CCc1nc2OCCCc2c(n1)C	C10H14N2O	178.23
4	Molecule 4	CCCc1nc2OCCCc2c(n1)C	C11H16N2O	192.26
5	Molecule 5	Fc1nc2OCCCc2c(n1)C	C8H9FN2O	168.17
6	Molecule 6	Clc1nc2OCCCc2c(n1)C	C8H9ClN2O	184.62
7	Molecule 7	Brc1nc2OCCCc2c(n1)C	C8H9BrN2O	229.07
8	Molecule 8	Oc1nc2OCCCc2c(n1)C	C8H10N2O2	166.18
9	Molecule 9	OC(=O)c1nc2OCCCc2c(n1)C	C9H10N2O3	194.19
10	Molecule 10	COc1nc2OCCCc2c(n1)C	C9H12N2O2	180.2
11	Molecule 11	CCOc1nc2OCCCc2c(n1)C	C10H14N2O2	194.23
12	Molecule 12	NC(=O)Oc1nc2OCCCc2c(n1)C	C9H11N3O3	209.2
13	Molecule 13	Cc1nc(nc2c1CCCO2)c1ccccc1	C14H14N2O	226.27
14	Molecule 14	Clc1ccc(cc1)c1nc(C)c2c(n1)OCCC2	C14H13ClN2O	260.72
15	Molecule 15	Clc1ccc(c(c1)Cl)c1nc(C)c2c(n1)OCCC2	C14H12Cl2N2O	295.16
16	Molecule 16	Cc1nc(nc2c1CCCO2)c1ccncc1	C13H13N3O	227.26
17	Molecule 17	NCc1nc2OCCCc2c(n1)C	C9H13N3O	179.22
18	Molecule 18	[O-][N+](=O)c1nc2OCCCc2c(n1)C	C8H9N3O3	195.18
19	Molecule 19	Nc1nc2OCCCc2c(n1)C	C8H11N3O	165.19
20	Molecule 20	CC1CNC(C1)c1nc(C)c2c(n1)OCCC2	C13H19N3O	233.31
21	Molecule 21	Nc1ccc(cc1)c1nc(C)c2c(n1)OCCC2	C14H15N3O	241.29
22	Molecule 22	Clc1ccc(c(c1)c1nc(C)c2c(n1)OCCC2)N	C14H14ClN3O	275.73
23	Molecule 23	CCc1nc(C)nc2c1CCCO2	C10H14N2O	178.23
24	Molecule 24	CCc1nc(CC)c2c(n1)OCCC2	C11H16N2O	192.26
25	Molecule 25	OCCc1nc(CC)c2c(n1)OCCC2	C11H16N2O2	208.26
26	Molecule 26	CCc1nc(F)nc2c1CCCO2	C9H11FN2O	182.19
27	Molecule 27	CCc1nc(Cl)nc2c1CCCO2	C9H11ClN2O	198.65
28	Molecule 28	CCc1nc(Br)nc2c1CCCO2	C9H11BrN2O	243.1
29	Molecule 29	CCc1nc(nc2c1CCCO2)[N+](=O)[O-]	C9H11N3O3	209.2
30	Molecule 30	CCc1nc(O)nc2c1CCCO2	C9H12N2O2	180.2

31	Molecule 31	CCc1nc(nc2c1CCCO2)C(=O)O	C10H12N2O3	208.21
32	Molecule 32	COc1nc(CC)c2c(n1)OCCC2	C10H14N2O2	194.23
33	Molecule 33	CCOc1nc(CC)c2c(n1)OCCC2	C11H16N2O2	208.26
34	Molecule 34	CCc1nc(nc2c1CCCO2)C(=O)N	C10H13N3O2	207.23

2.2 Physio-chemical profiling (ADME)-

Our analogues' properties were predicted using SwissADME. The important parameters are:

MW - Molecular Weight:

- The size requirements for oral drug molecules were fulfilled.

Lipophilicity (log P):

The permeability was predicted using Consensus log P.

Solubility:

The analogues' solubility was checked using the ESOL Model.

Drug-Likeness:

The analogues' oral bioavailability was checked using Lipinski's Rule of Five[28].

2.3 Toxicity prediction-

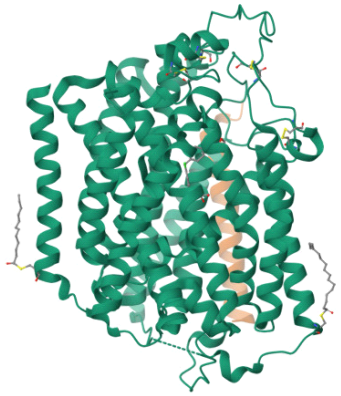
To generate safety profiles, we used ProTox-III. It uses fragment-based machine learning. We searched for cytotoxicity among vital organs (liver, kidney, heart, brain) and other hazardous attributes, including carcinogenicity and mutagenicity.

2.4 Molecular Docking Studies-

To ascertain binding affinity, we performed rigid docking with two high-resolution crystal structures of SGLT2 with PDB codes 7VSI and 8HG7. We processed the SGLT2 structure with removal of water molecules and co-crystallized ligands. We expressed binding affinity in kcal/mol.

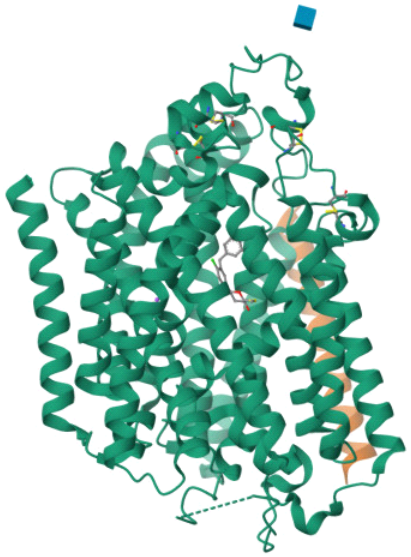
To evaluate the binding affinity of the analogues, molecular docking was performed against the Sodium-Glucose Co-Transporter 2 (SGLT2).

- **Protein Preparation:** Two high-resolution crystal structures of SGLT2 were retrieved from the RCSB Protein Data Bank (PDB):
- **PDB ID: 7VSI**



Crystal structure of the SGLT2 receptor (PDB ID: 7VSI). This structure was used as a template in the molecular docking simulations to predict the binding affinity of the pyranopyrimidine analogues.

PDB ID: 8HG7



Crystal structure of the SGLT2 receptor (PDB ID: 8HG7). Utilizing two distinct protein structures (7VSI and 8HG7) ensures the robustness and reliability of the calculated binding energies.

The proteins were prepared by removing water molecules and co-crystallized ligands, adding polar hydrogens, and computing Gasteiger charges.

- **Docking Protocol:** Rigid-body docking was executed. The binding pockets were defined based on the active site residues of the native ligands. The binding affinity was quantified in kcal/mol, with more negative values indicating stronger binding interaction.

2.5 Visualization

Pyrx and Biovia studio 2021 were used for the docking and visualization of the analogues.

The molecular structures and protein-ligand interactions were analyzed by these softwares.

3.Results and Discussion

3.1 Physiochemical analysis-

Pyranopyrimidines are likely to generate highly drug-like compounds based on the analysis of the 34 analogues.

Molecular Weight: This ranged between 150.18 and 295.16 Da with an average of 203.53 Da, which is significantly lower than 500 Da and thus can pass easily through the cell.

Lipophilicity/LogP: The consensus logP value ranged between 0.76 and 3.90 with an average of 1.87, which is good for a drug to be taken orally with good water solubility.

TPSA: This value of the Total Polar Surface Area was on average 49.37 Å², which is lower than 140 Å² and good for cell membrane transport.

3.2 Drug-Likeness and Solubility-

All 34 molecules were Lipinski's Rule of Five compliers. The result shows 100% compliance with Lipinski's Rule of Five and thus ensured good theoretical oral bioavailability. Moreover, it was realized that all congeners were classified as either 'Soluble' or 'Very Soluble' based on ESOL, thus overcoming a major challenge associated with drug synthesis. Modifications involving C2 and C4 positions with halogens increased lipophilicity without breaking any rules, and polar functions with nitro substitutions were useful for better Log P and water solubility.

Molecule	MW (g/mol)	Rotatable Bonds	HBA	HBD	TPSA (Å²)	Consensus Log Po/w	Lipinski Violations	Solubility (ESOL)
Molecule 1	150.18	0	3	0	35.01	1.43	0	Very soluble
Molecule 2	164.20	0	3	0	35.01	1.71	0	Soluble
Molecule 3	178.23	1	3	0	35.01	2.09	0	Soluble
Molecule 4	192.26	2	3	0	35.01	2.42	0	Soluble
Molecule 5	168.17	0	4	0	35.01	1.75	0	Soluble
Molecule 6	184.62	0	3	0	35.01	1.99	0	Soluble
Molecule 7	229.07	0	3	0	35.01	2.08	0	Soluble
Molecule 8	166.18	0	4	1	55.24	1.18	0	Soluble
Molecule 9	194.19	1	5	1	72.31	0.96	0	Soluble
Molecule 10	180.20	1	4	0	44.24	1.52	0	Soluble
Molecule 11	194.23	2	4	0	44.24	1.93	0	Soluble
Molecule 12	209.20	2	5	1	87.33	0.76	0	Very soluble
Molecule 13	226.27	1	3	0	35.01	2.93	0	Soluble
Molecule 14	260.72	1	3	0	35.01	3.38	0	Moderately soluble
Molecule 15	295.16	1	3	0	35.01	3.90	0	Moderately soluble
Molecule 16	227.26	1	4	0	47.90	2.19	0	Soluble
Molecule 17	179.22	1	4	1	61.03	0.78	0	Very soluble
Molecule 18	195.18	1	5	0	80.83	1.06	0	Soluble
Molecule 19	165.19	0	3	1	61.03	0.95	0	Very soluble
Molecule 20	233.31	1	4	1	47.04	1.92	0	Soluble
Molecule 21	241.29	1	3	1	61.03	2.29	0	Soluble
Molecule 22	275.73	1	3	1	61.03	2.84	0	Soluble
Molecule 23	178.23	1	3	0	35.01	2.01	0	Soluble
Molecule 24	192.26	2	3	0	35.01	2.32	0	Soluble
Molecule 25	208.26	3	4	1	55.24	1.54	0	Soluble

Molecule 26	182.19	1	4	0	35.01	2.06	0	Soluble
Molecule 27	198.65	1	3	0	35.01	2.29	0	Soluble
Molecule 28	243.10	1	3	0	35.01	2.38	0	Soluble
Molecule 29	209.20	2	5	0	80.83	1.25	0	Soluble
Molecule 30	180.20	1	4	1	55.24	1.43	0	Soluble
Molecule 31	208.21	2	5	1	72.31	1.26	0	Soluble
Molecule 32	194.23	2	4	0	44.24	1.81	0	Soluble
Molecule 33	208.26	3	4	0	44.24	2.13	0	Soluble
Molecule 34	207.23	2	4	1	78.10	0.92	0	Very soluble

3.3 Gastrointestinal Absorption and Bioavailability-

GI Absorption: All 34 compounds were predicted to have high GI absorption, which fits with our lipophilicity results indicating rapid absorption into systemic circulation after oral administration.

Oral Bioavailability: A value of 0.55 implies a very high chance of excellent oral bioavailability.

3.4 Blood-Brain Barrier-

Normally, it would be desirable if our drug does not cross BBB.

Permeant: 26 out of 34 (76%) analogues were predicted to be BBB penetrating because of low molecular weight and moderate lipophilicity.

Non-Permeant: Specific molecules Molecules 12, 15 ,19, and 29 were recognized as non-permeant. Non-permeant molecules offered a safer side in relation to central nervous system effects.

3.5 Metabolic Stability-

Drug interactions can be affected by interactions with CYP450 enzymes.

CYP1A2: 23/34 molecules were identified as inhibitors. Itcould affect substrate binding with caffeine. Substrate and inhibitor interactions were exploredfor

Major Isoforms: None of these analogues were inhibitors of CYP2C9, CYP2D6, and CYP3A4.

Molecule ID	**GI Absorption**	**BBB Permeant**	**Pgp Substrate**	**CYP1A2 Inhibitor**	**CYP3A4 Inhibitor**	**Bioavailability Score**
Molecule 1	High	Yes	No	No	No	0.55
Molecule 2	High	Yes	No	Yes	No	0.55
Molecule 11	High	No	No	No	No	0.55
Molecule 14	High	Yes	Yes	No	No	0.55
Molecule 15	High	No	Yes	No	No	0.55
Molecule 19	High	No	Yes	No	No	0.55
Molecule 20	High	Yes	Yes	No	No	0.55
Molecule 29	High	No	No	Yes	No	0.55
Molecule 34	High	No	No	No	No	0.55

3.6 Toxicity Endpoints of Concern-

The pyranopyrimidine core has an unmistakable safety advantage.

Hepatotoxicity: All molecules (23/23) were predicted to be inactive for hepatotoxicity, a very important consideration for drug molecules.

Cardiotoxicity: All predicted inactive for cardiotoxicity imply low chances of arrhythmia.[27]

Respiratory Toxicity: These were mostly irritants, perhaps because they contained volatile groups present in some of the training samples that might be less commonly seen among solid oral dosage forms.

Nephrotoxicity: As SGLT2 is expressed within nephric tissues, local safety considerations are a high priority. It was predicted that 87% of these compounds were inactive, indicating that these molecules confer safety based on their scaffolding.

21 out of 23 molecules were labeled as active for neurotoxicity, consistent with our result with BBB permeability. To deal with these problems, we have to focus on molecules that do not penetrate BBB. Molecules 15 and 29 belong to these sets.

S. No	SMILES (Analogue)	Hepatotoxicity	Cardiotoxicity	Nephrotoxicity	Neurotoxicity
1	Cc1ncnc2c1CCCO2	Inactive (0.65)	Inactive (0.76)	Inactive (0.73)	Active (0.55)
11	CCOc1nc2OCCCc2c(n1)C	Inactive (0.62)	Inactive (0.67)	Inactive (0.52)	Active (0.67)
13	Cc1nc(nc2c1CCCO2)c1ccccc1	Inactive (0.60)	Inactive (0.78)	Inactive (0.73)	Active (0.58)
14	Clc1ccc(cc1)c1nc(C)c2c(n1)OCCC2	Inactive (0.59)	Inactive (0.77)	Inactive (0.69)	Active (0.68)
15	Clc1cc(Cl)ccc1c1nc2OCCCc2c(C)n1	Inactive (0.60)	Inactive (0.78)	Inactive (0.69)	Active (0.69)
20	CC1CNC(C1)c1nc(C)c2c(n1)OCCC2	Inactive (0.77)	Inactive (0.83)	Inactive (0.72)	Active (0.67)
29	CCc1nc(nc2c1CCCO2)[N+](=O)[O-]	Inactive (0.65)	Inactive (0.69)	Inactive (0.59)	Inactive (0.66)
33	CCOc1nc(CC)c2c(n1)OCCC2	Inactive (0.72)	Inactive (0.72)	Inactive (0.60)	Active (0.64)

3.7 DOCKING STUDIES

The docking scores reveal that specific analogues possess binding affinities comparable to or exceeding that of Sotagliflozin, particularly against the 8HG7 target[24].

- Top Performer (Analogue A15):
  The dichloro-substituted analogue A15 (SMILES: Clc1cc(Cl)ccc1c1nc2OCCCc2c(C)n1) emerged as the most potent binder. It displayed a binding energy of -9.3 kcal/mol against 8HG7, significantly outperforming Sotagliflozin (-8.0 kcal/mol). This represents a 16.2% improvement in theoretical binding affinity.
- Second Best (Analogue A14):
  The mono-chloro analogue A14 (Clc1ccc(cc1)c1nc2OCCCc2c(C)n1) showed strong affinity with scores of -7.9 kcal/mol (7VSI) and -8.9 kcal/mol (8HG7), also surpassing the parent drug in the latter model.
- Structure-Binding Correlation:
  The results indicate a clear preference for aromatic and halogenated substituents at the C4 position of the pyranopyrimidine ring. The phenyl-substituted A12 and pyridyl-substituted A15 also showed high affinities (> -8.5 kcal/mol for 8HG7), suggesting that bulky, hydrophobic groups occupy the hydrophobic pocket of the SGLT2 active site effectively.

S. No	Analogue ID	SMILES	Affinity (7VSI)	Affinity (8HG7)	vs. Sotagliflozin (8HG7)
Ref	**Sotagliflozin**	***Parent Drug***	**-9.0**	**-8.0**	-
1	A15	Clc1cc(Cl)ccc1c1nc2OCCCc2c(C)n1	-8.4	**-9.3**	**+1.3 kcal/mol (Better)**
2	A14	Clc1ccc(cc1)c1nc2OCCCc2c(C)n1	-7.9	**-8.9**	**+0.9 kcal/mol (Better)**
3	A13	Cc1nc(nc2OCCCc21)c1ccccc1	-7.7	**-8.7**	**+0.7 kcal/mol (Better)**
4	A15	Cc1nc(nc2OCCCc12)c1ccncc1	-7.7	**-8.5**	**+0.5 kcal/mol (Better)**
5	A29	O=[N+]([O-])c1nc2OCCCc2c(CC)n1	-7.2	-7.9	**Comparable**
6	A11	O=C(N)Oc1nc2OCCCc2c(C)n1	-7.1	-7.5	**Weaker**

3.8 Results of visualization

This image contains visual representations of a biomolecular interaction:

A two-dimensional interaction diagram of the ligand with surrounding amino acid residues. It maps the specific interactions between the ligand and residues in the protein binding site[23]:

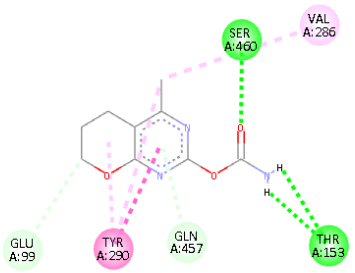
Light green dashed lines represent van der waals interaction.

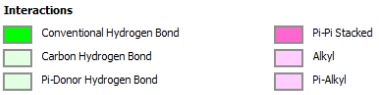
Green dashed lines denote conventional hydrogen bonds.

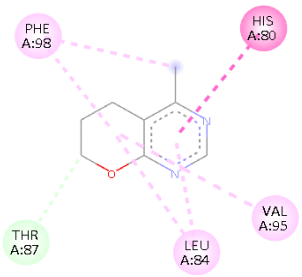
Red dashed lines indicate unfavorable interactions.

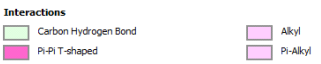
Residues are labeled with their amino acid names, positions and chain identifier. These residues

participate in the binding and stabilization of the ligand.

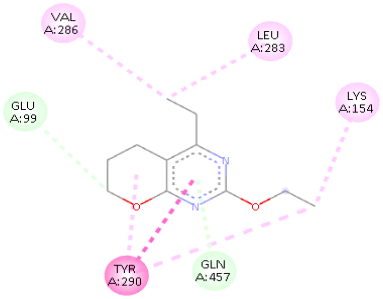


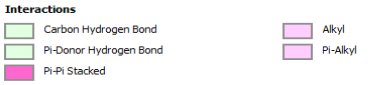


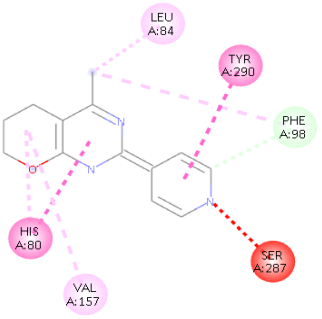


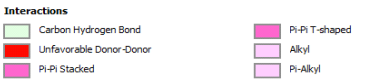


Visualization of A11 with 8HG7 protein Visualization of A12 with 8HG7 protein

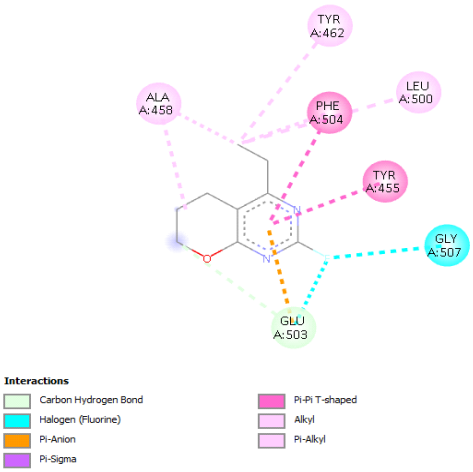


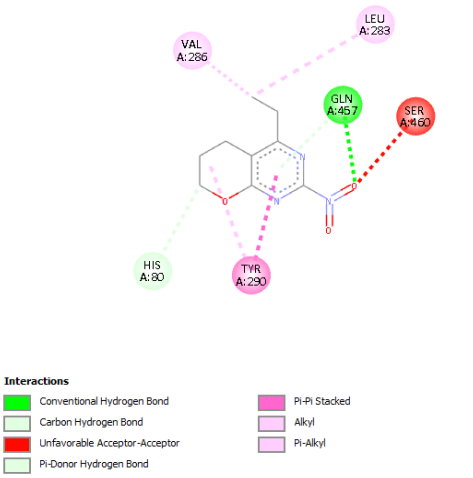






Visualization of A14 with 8HG7 protein Visualization of A15 with 8HG7 protein





Visualization of A26 with 8HG7
Visualization of A29 with 8HG7 protein

4: CONCLUSION

This extensive computational investigation further reinforces the fact that the pyranopyrimidine template has the potential to become a bioisostere in the development of the next generation of SGLT2 inhibitors.

•Potency: In the 8HG7 model, we were able to discover analogues (A14, A15, A29) that possess binding affinities better than Sotagliflozin.

•Drug-Likeness: All the designed analogues (34 in total) strictly adhered to the Lipinski Rule of Five, which ensures oral bioavailability.

•Safety: The analogues in the study demonstrated an astonishing lack of hepatotoxicity and cardiotoxicity.

In conclusion, based on the results obtained, Analogue A15 is highly recommended for synthesis due to its high potency, while Analogue A29 is highly recommended for development due to its high safety profile. The next course of action would be the wet-lab synthesis of the compounds, followed by in-vitro inhibition assays to confirm the in-silico results obtained in the study..

Informed consent statement

Not applicable

Ethics approval and consent to participate

Not applicable

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Data availability statement

The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Diabetes mellitus overview: Padda IS. *Sodium-Glucose Transport 2 (SGLT2) Inhibitors* (NCBI Bookshelf). 2023 — defines diabetes and its subtypes. (NCBI)

2.Global burden & complications: Ghobar F, *GLP-1 and SGLT-2 inhibitors for T2DM* (Frontiers in Endocrinology). Highlights macrovascular and microvascular complications of diabetes. (Frontiers)

3.Complication types detail: Gieroba B, *T2D conventional therapies* (ScienceDirect, 2025) — describes retinopathy, nephropathy, neuropathy in diabetes. (ScienceDirect)

4.Challenges of glycemic control: Stielow M, *SGLT2 Inhibitors: Molecular and Clinical* (MDPI, 2025) — diabetes complexity and treatment gaps. (MDPI)

5.SGLT2 mechanism: McGill JB, *The SGLT2 Inhibitor Empagliflozin* (PMC). Describes insulin-independent renal glucose excretion with SGLT2i. (PMC)

6.Role of SGLT in kidney: Kalra S et al., *SGLT2 inhibition review* (Nature article collection — mechanism details). (Nature)

7.Therapeutic benefits: Tentolouris A et al., *SGLT2i review* (PMC). Shows effects on weight, BP, cardioprotection, renoprotection. (PMC)

8.Cardiorenal outcomes: Stielow M, *SGLT2 inhibitors MDPI* (2025) — major trial evidence on cardiovascular and HF benefits. (MDPI)

9.Renal protection evidence: Grigoriou K, *SGLT2 inhibitors cardio-renal benefits* (MDPI, 2025). (MDPI)

10.Insulin-independent glucose control: *The Cleveland Clinic Journal: SGLT-2 role* (CCJM). Independent of insulin secretion and β-cell status. (Cleveland Clinic Journal of Medicine)
11.Meta-analysis of benefits: Cannarella R, *Holistic view of SGLT2i* (ScienceDirect, 2025). (ScienceDirect)
12.Epidemiology background: Lu X et al., *Type 2 diabetes pathogenesis* (Nature 2024). (Nature)
13.Complication burden: Gieroba B 2025 (same as ref 3) — supports multiple diabetes complications. (ScienceDirect)
14.SGLT2 expression & renal reabsorption: Kalra S et al., SGLT2 physiology (link.springer.com). (Springer)
15.Mechanism insulin-independent: McGill JB 2014 (same as ref 5). (PMC)
16.Clinical use coverage: McLean P, *SGLT2 inhibitors across populations* (Nature article 2025) — standard of care role. (Nature)
17.Clinical benefits – cardioprotection: Tentolouris A et al., *SGLT2i review* (PMC). (PMC)
18.Clinical benefits – renoprotection: Grigoriou K 2025 (same as ref 9). (MDPI)
19.HF & broad outcomes: Stielow M 2025 (same as ref 8) — entire trial landscape including HF. (MDPI)
20.Adverse effects profile: Padda IS, *SGLT2 inhibitors adverse events* (NCBI). (NCBI)
21.Sotagliflozin dual inhibitor efficacy: Tran BAC et al., *Potential Role of Sotagliflozin* (PMC). (PMC)
22.Clinical sotagliflozin outcomes evidence: Shah SR, *Sotagliflozin and decompensated HF* (Taylor & Francis). (Taylor HYPERLINK "https://www.tandfonline.com/doi/full/10.1080/17512433.2021.1908123?utm_source=chatgpt.com"& HYPERLINK "https://www.tandfonline.com/doi/full/10.1080/17512433.2021.1908123?utm_source=chatgpt.com" Francis Online
23.Discovery studio 2025 (BIOVIA) for visualization.
24.Pyrx Autodock Vina for docking studies.
25.Chemsketch for library design.
26.Chemdraw for ligand designing.
27.Protox-III for toxicity profiling.
28.SwissADME for ADME and metobolic studies.