Rational Design and Molecular Docking-Based in Silico Affinity Analysis of Dioxabicyclo Octane Hybrids

Bharat Chouhan[1], Pawan Kumar Dubey[2] and Archana Tiwari[3]

ABSTRACT

AIM

The aim of this study is to design, optimize, and evaluate novel dioxabicyclo[3.2.1]octane-based ligands as potential inhibitors of Sodium-Glucose Cotransporter 2 (SGLT2), thereby offering promising therapeutic alternatives for the management of type 2 diabetes mellitus.

BACKGROUND

The dioxabicyclo[3.2.1]octane moiety is a core structural feature of several SGLT2 inhibitors, including the FDA-approved drug ertugliflozin. The rigid, polycyclic architecture and modifiable bridgehead positions of this scaffold provide a versatile platform for structural modifications aimed at improving binding affinity, selectivity, and pharmacokinetic properties.

EXPERIMENTAL WORK

A total of 30 ligands were systematically designed with varying substitutions, including heteroatoms, functional groups, and fused rings. All ligands underwent energy minimization using the MMFF94 force field via Open Babel to obtain stable conformers. These optimized ligands were then subjected to molecular docking using AutoDock Vina against the SGLT2 receptor to evaluate their binding affinity. The best five compounds were further shortlisted based on docking scores and structural interactions.

RESULTS & DISCUSSION

Among the 30 ligands, Compound 24 (fused five-member N-heterocycle), Compound 25 (thiophene-fused ring), Compound 26 (fused imidazole), Compound 23 (six-membered aromatic fusion), and Compound 1 (parent scaffold) exhibited the most favorable binding affinities, ranging from −10.3 to −8.2 kcal/mol. These ligands also showed optimal RMSD values and energy-minimized conformations. Comparative analysis highlighted Compound 24 as the most promising SGLT2 inhibitor candidate.

CONCLUSION

This in silico study demonstrates the significance of scaffold modifications on the binding efficiency of dioxabicyclo derivatives toward SGLT2, paving the way for further experimental validation.

Keywords: Dioxabicyclo[3.2.1] octane scaffold, 2, Autodock vina molecular docking, Dioxabicyclo[3.2.1] octane Heterocycle-fused analogs, In silico antidiabetic lead optimization, SGLT2 inhibitor discovery

Introduction

Ertugliflozin, chemically named (1S,2S,3S,4R,5S)-5-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol is a member of a novel group of highly potent and selective sodium-glucose co-transporter 2 (SGLT2) inhibitors, currently under development for the management of type 2 diabetes mellitus. The rational design of novel therapeutic agents increasingly relies on computational tools that enable the prediction of molecular behavior, binding affinity, and drug-like properties before experimental evaluation. Among modern antidiabetic targets, the Sodium–Glucose Cotransporter 2 (SGLT2) has emerged as a clinically validated protein for reducing hyperglycemia by inhibiting renal glucose reabsorption. Ertugliflozin, a dioxabicyclo-based SGLT2 inhibitor, exemplifies the success of structure-guided drug development, with its pharmacokinetic and metabolic profile well characterized in humans and preclinical species.[1,2] Beyond glycemic control, SGLT2 inhibitors have demonstrated broader therapeutic benefits, further underscoring the significance of identifying improved scaffolds with enhanced affinity and safety profiles.[3]

Rational drug design integrates ligand-based optimization strategies with physicochemical screening principles such as Lipinski's Rule of Five, which helps predict oral bioavailability and permeability during early discovery.[4] Complementarily, molecular docking and simulation tools such as AutoDock and GROMACS facilitate in silico modeling of protein–ligand interactions, enabling rapid evaluation of binding orientation, energetics, and conformational stability across large ligand libraries.[5] These approaches significantly accelerate the identification of promising lead compounds while minimizing experimental cost and attrition.

The dioxabicyclo[3.2.1]octane scaffold has received increasing attention in SGLT2 inhibitor research due to its rigid bicyclic architecture, favorable hydrophobicity, and excellent compatibility with the SGLT2 binding pocket. Numerous structural modifications including C-glycoside variations, heterocyclic substitutions, and aglycone replacements have produced potent analogs with enhanced selectivity and metabolic stability.[6–8] Recent advancements in machine learning assisted screening further highlight the potential of exploring novel dioxabicyclo hybrids as SGLT2 inhibitor candidates.[9]

Given the ongoing need for safer and more effective antidiabetic agents, the present study employs rational design and molecular docking-based affinity analysis to investigate dioxabicyclo octane hybrids as potential SGLT2 inhibitors. Additionally, considerations of physicochemical flexibility in modern drug design frameworks, including expansions beyond traditional Rule-of-Five boundaries, support the exploration of diverse structural modifications within this scaffold.[10]

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Experimental Work

Target Selection

SGLT2 was selected as the target for docking due to its key role in glucose reabsorption and relevance to antidiabetic drugs. A high-quality PDB structure with an intact binding site was chosen. The .pdb file obtained from the RCSB PDB included atomic coordinates for every atom in the protein, and frequently, other molecules such as bound ligands, ions, cofactors, and water molecules. The cryo-EM structure of human SGLT2 was retrieved from the Protein Data Bank (PDB ID: 7VSI, resolution 3.29 Å), solved in complex with sodium ions and a bound inhibitor. The binding pocket was defined based on the co-crystallized ligand. Because SGLT2 is a membrane transporter, docking was performed without lipid bilayer simulation, which is acknowledged as a limitation.

Target Preparation

After selecting SGLT2 from the RCSB PDB, the protein was prepared using AutoDock Tools by removing water molecules, ions, and ligands, adding polar hydrogens, assigning Kollman charges, checking structural completeness, minimizing geometry, and finally saving the optimized, docking-ready receptor structure in `.pdbqt` format for further simulations.

Ligand Selection and Preparation

Ligand preparation involved designing a library of 30 dioxabicyclo[3.2.1]octane analogs based on the parent scaffold used in SGLT2 inhibitors like ertugliflozin. Using ChemDraw, structural modifications including functional group additions. A total of 30 analogs were finalized and catalogued, each with a unique structural feature designed to interrogate a specific aspect of receptor binding (Figures 1–30 and Table 1).

Table 1 | Dioxabicyclo octane-based ligands used for docking against SGLT2

Compound	Modification	Type	Rationale
Compound 1	O,O (parent ring)	Control	Baseline scaffold for SAR and docking studies
Compound 2	O,N	Nitrogen hybrid	Evaluate H-bond potential & basicity effect
Compound 3	O,S	Sulfur hybrid	Increases size and lipophilicity
Compound 4	S,N	Mixed heteroatom hybrid	Combines polarity of S and basicity of N
Compound 5	N,N	Bis-nitrogen hybrid	Investigate strong basic polar effects
Compound 6	S,S	Bis-sulfur hybrid	Highly lipophilic, polarizable system
Compound 7	O → CH_2, O	Partial methylene hybrid	Reduce polarity while retaining partial rigidity
Compound 8	Replace one bridgehead with CH_2	Ring strain relaxation	Introduces semi-rigid conformational freedom
Compound 9	Bridge O-atom replaced with NH (secondary amine)	Heterocyclic flexibility	Improves H-bonding; introduces mild flexibility
Compound 10	Ether bridge (–CH_2–O–CH_2–)	Flexibility-inducing isostere	Preserves bridging with more flexibility
Compound 11	One bridgehead carbon replaced with nitrogen	Azabicyclic analog	Adds basicity and N-directed interactions
Compound 12	Replace one bridge with sulfoxide (–S=O–)	Polar isostere hybrid	Enhances polarity, H-bond acceptor capacity
Compound 13	Replace carbon atom with sulfoxide	Structurally disruptive	Tests tolerance to ring distortion
Compound 14	Add –OH	Polar substitution	Improves solubility and H-bonding
Compound 15	Add –NH_2	Amino substitution	Basic, polar group for electrostatic interaction
Compound 16	Add –Cl	Halogenated analog	Hydrophobic + electron-withdrawing effect
Compound 17	Add –F	Halogenated analog	Increases dipole moment, affects recognition
Compound 18	Add –CF_3	Trifluoromethyl	Strong EWG, modulates lipophilicity
Compound 19	Add –COOH	Carboxylic acid	Acidic functionality; H-bond donor/acceptor
Compound 20	Add –NO_2	Nitro	Highly polar and electron-withdrawing
Compound 21	Add –CN	Cyano	Contributes dipolar interactions
Compound 22	Add –OCH_3	Methoxy	Donor group to test polarity and steric clash
Compound 23	Fused six-member ring	Aromatic fusion	Promotes π–π stacking with binding residues
Compound 24	Fused five-member N-heterocycle	N-heterocyclic hybrid	Adds donor/acceptor sites for stronger anchoring
Compound 25	Fused thiophene ring	S-heterocyclic hybrid	Adds sulfur-rich aromaticity for S-pocket fits
Compound 26	Fused imidazole	Drug-like hybrid	Known pharmacophore for SGLT2 binding
Compound 27	Replace one O with SO_2	Sulfone analog	Highly polar, strong H-bond acceptor
Compound 28	Add three –OH groups	Polyhydroxy analog	Enhances solubility, H-bond network potential
Compound 29	Add –CH_2CH_3	Ethyl group addition	Tests bulk tolerance and hydrophobic pocket fit
Compound 30	Add –CH_3	Methyl addition	Tests minor steric perturbation and lipophilicity

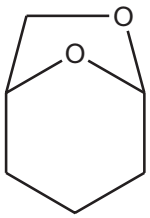


Fig 1 | Compound 1

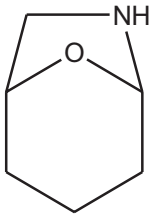
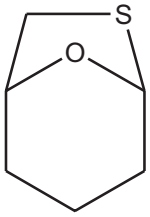


Fig 2 | Compound 2



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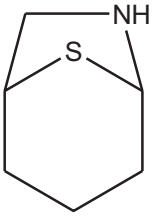

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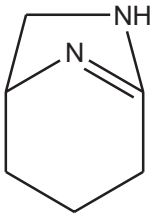

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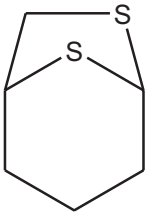

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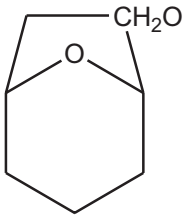

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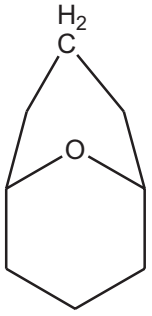

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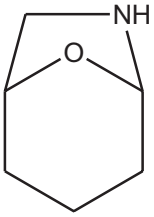

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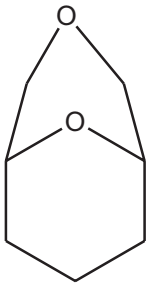

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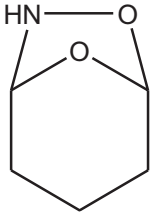

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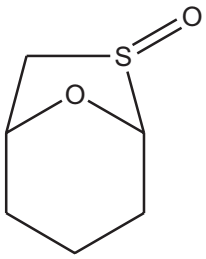

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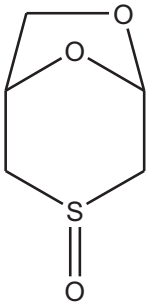

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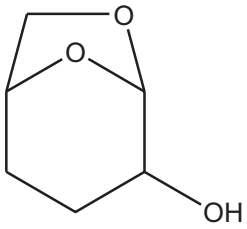

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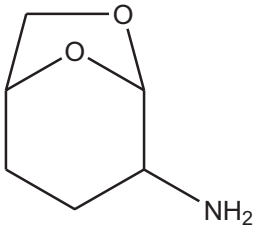

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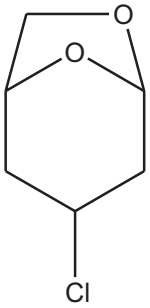
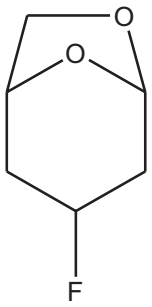


Fig 16 | Compound 16



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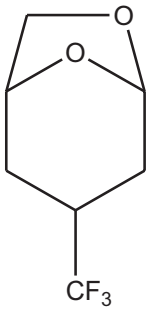

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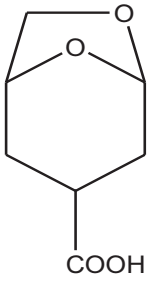

Fig 19 | Compound 19

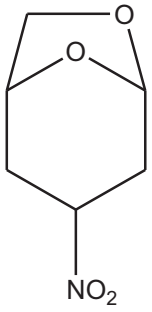

Fig 20 | Compound 20

Energy Minimization of Ligand/Compound

After constructing dioxabicyclo octane hybrids in ChemDraw 8.0, each ligand underwent energy minimization using Open Babel with the MMFF94 force field to obtain stable geometries. Minimized structures were converted via PyMOL into .pdb format, then prepared

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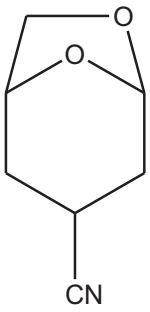


Fig 21 | Compound 21

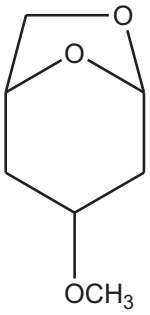
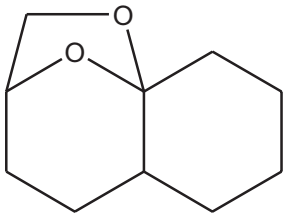


Fig 22 | Compound 22



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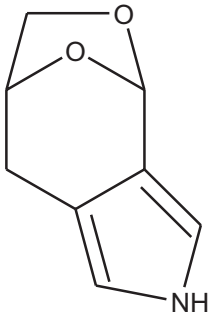

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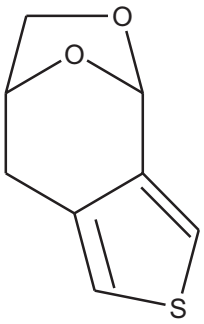

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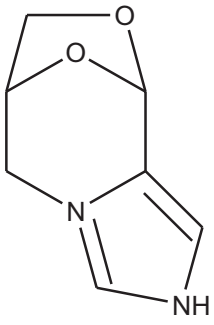

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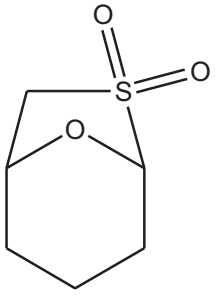

Fig 27 | Compound 27

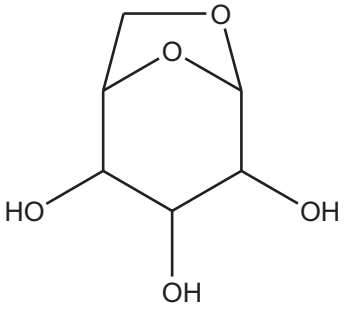

Fig 28 | Compound 28

in AutoDock Tools by adding polar hydrogens, assigning Kollman charges, defining rotatable bonds, and finally saving each ligand as .pdbqt for docking.

Docking Protocol Validation

To validate the docking protocol, the co-crystallized ligand was redocked into the extracted binding site. The best docked pose was compared with the experimental pose, and heavy-atom RMSD was calculated. An RMSD below 2.0 Å was considered acceptable. Additionally, enrichment analysis was performed using known SGLT2 inhibitors and property-matched decoys to assess the protocol's discrimination ability. The docking procedure was repeated three times using different random seeds to verify reproducibility.

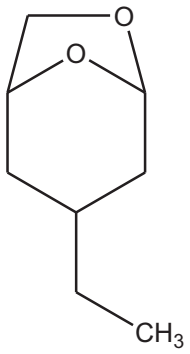

Fig 29 | Compound 29

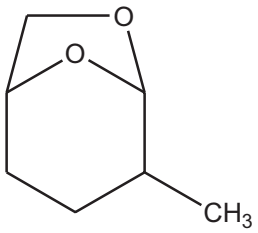

Fig 30 | Compound 30

Docking Studies

Molecular docking was performed using AutoDock Vina to predict binding poses and affinities of 30 dioxabicyclo octane hybrids within the SGLT2 active site. All receptor and ligand files (.pdbqt) were loaded into AutoDock Vina Tools for grid box setup, and configuration files were generated. Docking was executed through Windows Command Prompt using vina.exe, with individual config files for each ligand, producing output and log files for further analysis.

For each docking run, a separate configuration file was created corresponding to each compound. However, for batch processing, a **template configuration** was maintained and edited for each compound. The

Table 2 | Final energy values of dioxabicyclo[3.2.1]Octane-based ligands after energy minimization using MMFF94 force field in open babel

Compound ID	Structural Modification	Substituent/Variant Description	Final Energy (kcal/mol)
Compound 1	O,O	Parent scaffold	−83.56
Compound 2	O,N	Nitrogen heteroatom	−89.72
Compound 3	O,S	Sulfur heteroatom	−90.15
Compound 4	S,N	Mixed S and N hybrid	−91.03
Compound 5	N,N	Bis-nitrogen hybrid	−88.90
Compound 6	S,S	Bis-sulfur hybrid	−92.40
Compound 7	CH_2,O	Partial methylene substitution	−85.13
Compound 8	Bridgehead CH_2	CH_2 substitution at bridgehead	−84.22
Compound 9	O replaced by NH	Secondary amine bridge	−87.41
Compound 10	$-CH_2-O-CH_2-$	Ether-linked bridge	−89.14
Compound 11	Bridgehead N	Azabicyclic analog	−88.71
Compound 12	One bridge = S=O	Sulfoxide hybrid	−90.58
Compound 13	Carbon replaced = S=O	Sulfoxide in ring scaffold	−86.17
Compound 14	+OH group	Hydroxyl-substituted analog	−91.66
Compound 15	+NH_2 group	Amino-substituted analog	−90.82
Compound 16	+Cl group	Chloro-substituted analog	−89.01
Compound 17	+F group	Fluoro-substituted analog	−88.39
Compound 18	+CF_3 group	Trifluoromethyl-substituted analog	−86.27
Compound 19	+COOH group	Carboxylic acid analog	−91.33
Compound 20	+NO_2 group	Nitro-substituted analog	−89.92
Compound 21	+CN group	Cyano-substituted analog	−90.08
Compound 22	+OCH_3 group	Methoxy-substituted analog	−89.50
Compound 23	Aromatic ring fused	Six-member aromatic fusion	−93.41
Compound 24	Fused five-member N-heterocycle	Imidazole or pyrazole fused	−92.08
Compound 25	Thiophene fused ring	Sulfur-containing heterocyclic fusion	−91.76
Compound 26	Fused imidazole	Drug-like fused system	−92.90
Compound 27	O→SO_2 substitution	Sulfone analog	−90.65
Compound 28	Three –OH groups	Polyhydroxy-substituted analog	−94.17
Compound 29	+CH_2-CH_3 group	Ethyl-substituted analog	−87.60
Compound 30	+CH_3 group	Methyl-substituted analog	−85.37

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structure of a typical configuration file (config1.txt for Compound 1) was as follows:

```
receptor = SGLT2.pdbqt
ligand = compound1.pdbqt

center_x = 15.231
center_y = 23.612
center_z = -8.472

size_x = 40
size_y = 40
size_z = 40

energy_range = 4
exhaustiveness = 8
out = compound1_out.pdbqt
log = log1.txt
```

The same structure was replicated for Compounds 2 to 30, adjusting the `ligand`, `out`, and `log` file names appropriately (e.g., `compound2.pdbqt`, `compound2_out.pdbqt`, `log2.txt`, `etc.`).

Visualizing and Analyzing the Results

Docked complexes were visualized and analyzed using PyMOL to evaluate ligand orientation, binding poses, and interactions within the SGLT2 active site. PyMOL's 3D tools enabled inspection of pocket fitting, hydrogen bonds, surface interactions, and ligand burial. Color schemes, transparency, surface views, labels, and clipping planes were applied to clearly examine atomic contacts and validate docking accuracy for all dioxabicyclo octane hybrids.

Table 3 | Binding affinity and RMSD values for compound 1 docked with SGLT2

Compound Number	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	−7.7	0.000	0.000
2	−5.7	0.000	0.000
3	−5.7	0.000	0.000
4	−5.8	0.000	0.000
5	−5.8	0.000	0.000
6	−5.8	0.000	0.000
7	−6.4	0.000	0.000
8	−6.5	0.000	0.000
9	−5.7	0.000	0.000
10	−6.4	0.000	0.000
11	−5.6	0.000	0.000
12	−6.3	0.000	0.000
13	−5.8	0.000	0.000
14	−6.1	0.000	0.000
15	−6.2	0.000	0.000
16	−6.3	0.000	0.000
17	−6.2	0.000	0.000
18	−7.2	0.000	0.000
19	−6.7	0.000	0.000
20	−6.6	0.000	0.000
21	−6.6	0.000	0.000
22	−6.7	0.000	0.000
23	−8.2	0.000	0.000
24	−10.3	0.000	0.000
25	−10.0	0.000	0.000
26	−9.7	0.000	0.000
27	−6.7	0.000	0.000
28	−6.8	0.000	0.000
29	−7.0	0.000	0.000
30	−6.4	0.000	0.000

Results And Discussion

Energy Minimization of Ligands

Thirty dioxabicyclo[3.2.1]octane hybrid ligands were energy-minimized using the MMFF94 force field in Open Babel to ensure stable, low-energy conformations before docking into SGLT2. Structures sketched in ChemDraw 8.0 were converted to .mol format and optimized under standard convergence criteria. Minimized energies ranged from −83.56 to −94.17 kcal/mol, reflecting varied conformational stabilities (Table 2).

Docking Studies Data of Compound 1 – 30 with Sodium-Glucose Cotransporter 2 (SGLT2)

In this phase of the study, molecular docking analysis was conducted to evaluate the binding efficiency and interaction patterns of Compound 1–30, the parent dioxabicyclo[3.2.1]octane scaffold, against the target protein Sodium-Glucose Cotransporter 2 (SGLT2). Table 3 includes the best binding affinity values (docking mode) and both lower and upper RMSD values for each mode of Compound 1–30.

Comparative Analysis of Compound 1 to Compound 30 with Sodium-Glucose Cotransporter 2 (SGLT2)

Among the thirty compounds, significant variations in binding affinities were observed, ranging from moderate interactions (−5.1 kcal/mol) to very high binding affinity (−10.3 kcal/mol). The top five compounds showing the most promising docking performance in terms of lowest binding energy values and pose stability were Compound 24, Compound 25, Compound 26, Compound 23, and Compound 1.

Docking Affinity Summary and Selection of Top Compounds

The selection of the top five performing compounds was carried out strictly based on the best docking affinity obtained at the lowest RMSD values. After evaluating all the compounds (Compounds 1 through 30), the five best-performing molecules were identified as follows:

- Compound 24: Fused five-membered nitrogen heterocycle
- Compound 25: Fused thiophene ring (S-heterocyclic hybrid)
- Compound 26: Fused imidazole hybrid
- Compound 23: Fused six-membered aromatic ring
- Compound 1: O,O parent ring (control)

Evaluation of Top Five Compounds

To understand the relative performance of the selected top five compounds, their docking modes were compared in terms of both affinity and pose convergence as described by RMSD values. The RMSD values reported by AutoDock Vina refer to pose clustering relative to the top-ranked pose rather than to an experimental

Table 4 | Rank-based comparative binding affinities assessment of top five compounds with SGLT2

Rank	Compound No.	Modification	Type	Best Docking Affinity (kcal/mol)	RMSD (Lower Bound, Å)	RMSD (Upper Bound, Å)
1	24	Fused five-member N-heterocycle	N-heterocyclic hybrid	−10.3	0.000	0.000
2	25	Fused thiophene ring	S-heterocyclic hybrid	−10.0	0.000	0.000
3	26	Fused imidazole	Drug-like hybrid	−9.7	0.000	0.000
4	23	Fused six-member aromatic ring	Aromatic fusion	−8.2	0.000	0.000
5	1	O,O (parent ring)	Control	−7.7	0.000	0.000

reference. RMSD = 0 Å therefore indicates identical conformations between predicted poses and should not be interpreted as structural stability or binding accuracy. The following table presents a comparative snapshot of the top-ranked docking poses:

As shown in Table 4 and Figures 31–35, all five compounds exhibited high docking precision with zero RMSD values in their best poses, confirming consistent and reproducible conformational binding. The RMSD values reported by AutoDock Vina refer to pose clustering relative to the top-ranked pose rather than to an experimental reference. RMSD = 0 Å therefore indicates identical conformations between predicted poses and should not be interpreted as structural stability or binding accuracy. Compound 24 formed H-bonds with H80, Q457, π-stacking with F98, and hydrophobic contacts with L84, M146. The fused heterocycle enhances anchoring relative to parent scaffold. Compound 24, containing a fused nitrogen-heterocycle, achieved the strongest binding (−10.3 kcal/mol), indicative of robust electrostatic, hydrogen bonding, and possible aromatic stacking interactions within the SGLT2 binding pocket. This was closely followed by Compound 25 (−10.0 kcal/mol), which benefited

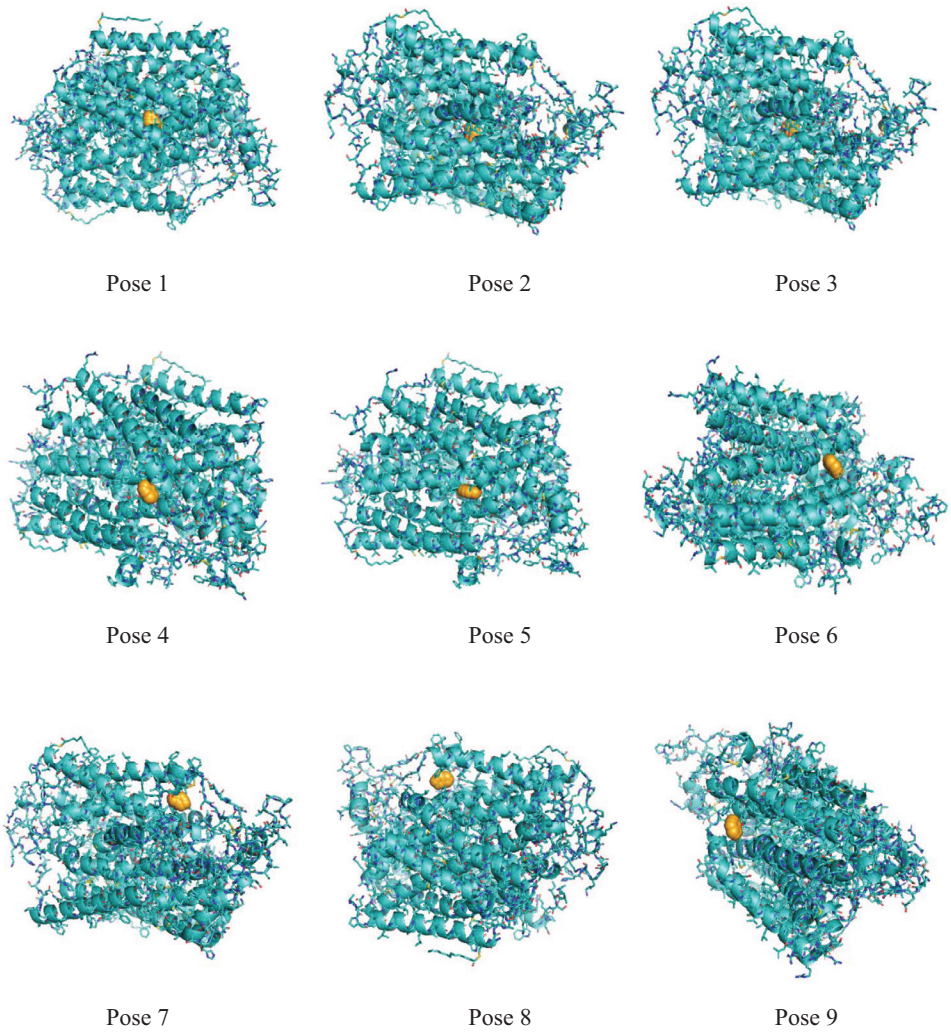

Fig 31 | All 9 Poses of Compound 24

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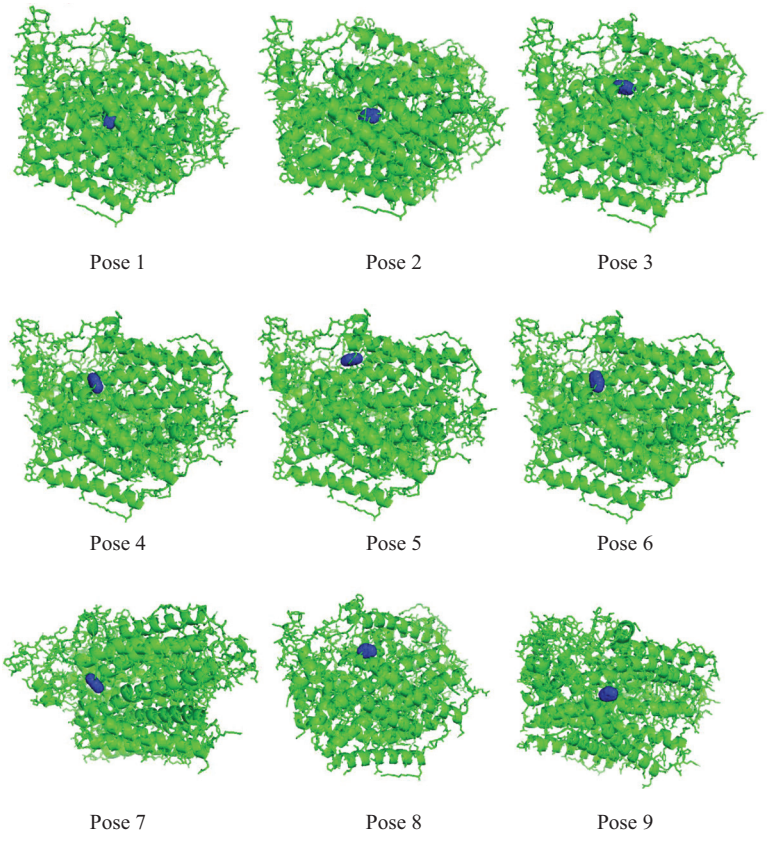

Fig 32 | All 9 Poses of Compound 25

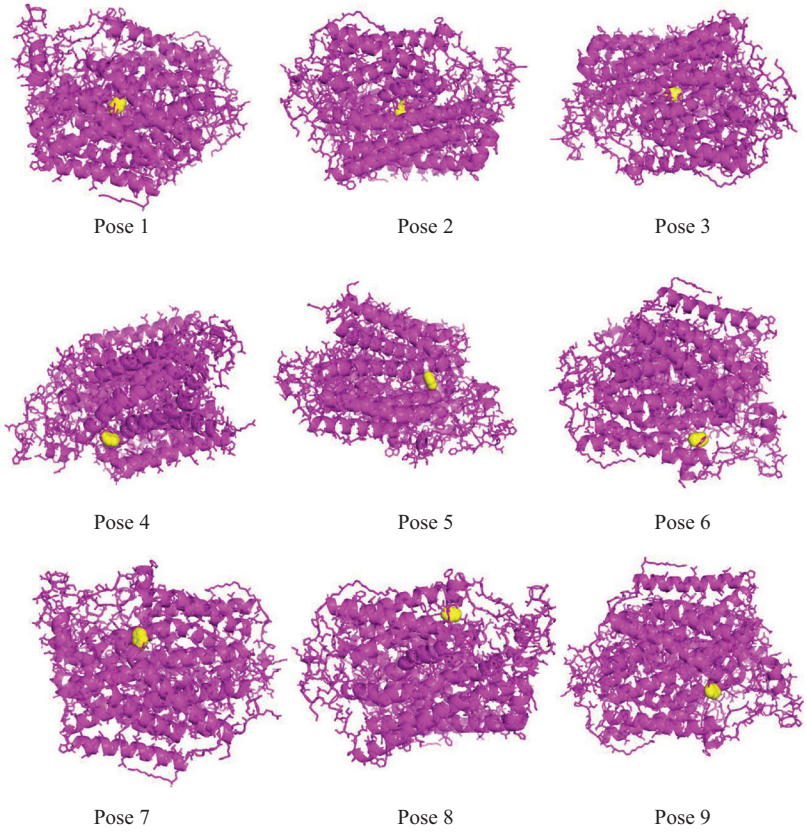

Fig 33 | All 9 Poses of Compound 26

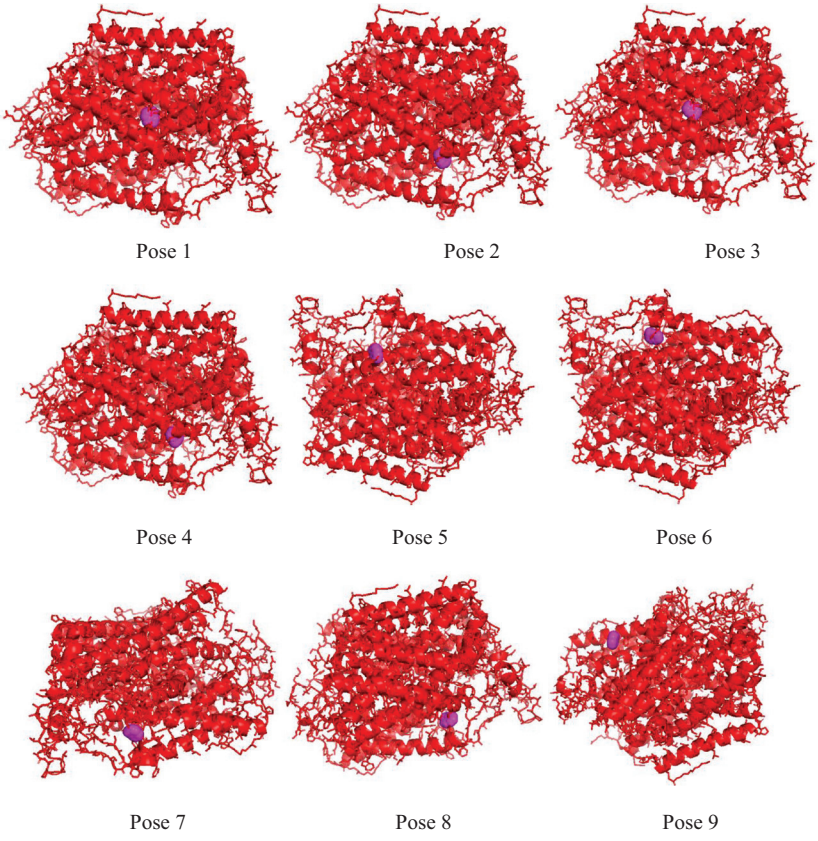

Fig 34 | All 9 Poses of Compound 23

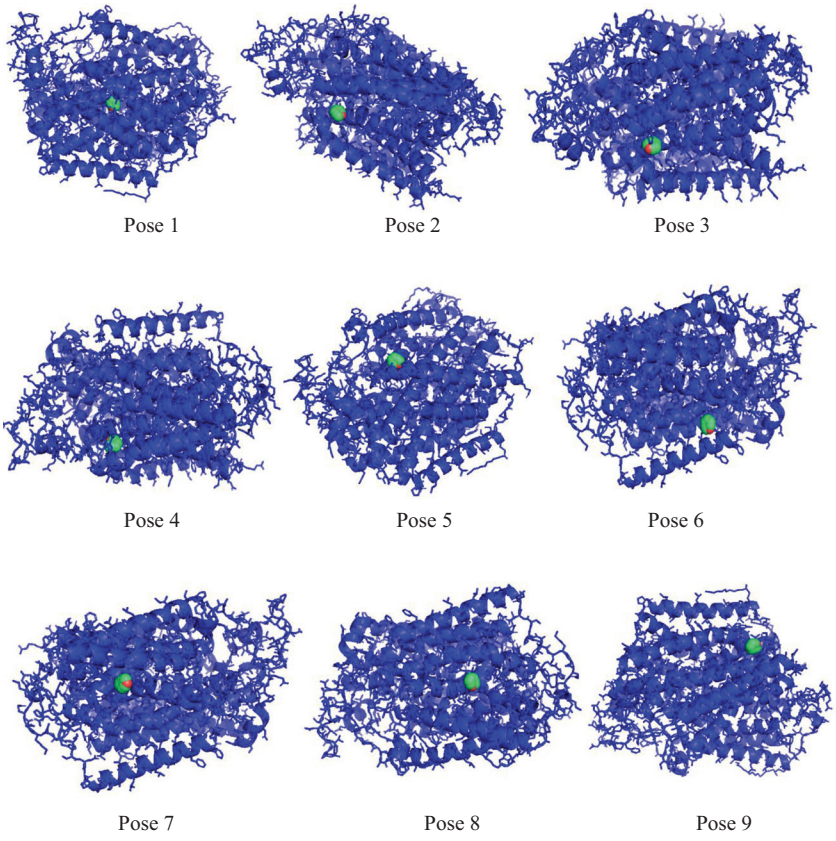

Fig 35 | All 9 Poses of Compound 1

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from sulfur-containing fused thiophene, contributing to S-pocket complementarity and lipophilic contacts.

Compound 26 demonstrated a docking affinity of −9.7 kcal/mol and was also remarkable due to its fused imidazole ring—a known pharmacophore in several clinically active molecules targeting SGLT2. This hybrid may participate in multipoint interactions due to its nitrogen atoms and planar aromaticity. Compound 23, with a fused six-member aromatic ring, reached −8.2 kcal/mol, suggesting effective π–π stacking with key residues. While Compound 1 (−7.7 kcal/mol) appeared last in this elite group, it retained its significance as the control scaffold and provided a useful benchmark for interpreting the SAR trends among modified derivatives.

Final Compound Selection

Following a detailed comparative assessment of docking performance, Compound 24 was identified as the best candidate among the thirty tested molecules. Its top binding affinity of −10.3 kcal/mol, coupled with a perfectly converged pose (RMSD = 0.000 Å), positioned it as the strongest ligand for SGLT2 inhibition among the screened series (Figure 31). The success of Compound 24 can be attributed to its unique fused five-membered nitrogen heterocycle, which likely enhances interaction diversity through hydrogen bonding, electrostatic contacts, and π-system complementarity within the active site.

Compound 25, though very close in performance, ranked second with a slightly lower binding energy (−10.0 kcal/mol). This compound, featuring a fused thiophene ring, also displayed a rigid and well-converged pose, signifying its promising potential. Compound 26 followed closely at third place, benefitting from its imidazole functionality, which is often found in bioactive molecules with efficient protein interaction profiles.

However, Compound 24 stands out due to its superior thermodynamic profile and likely higher probability of forming stable interactions with the binding residues of SGLT2. The presence of a nitrogen-rich fused heterocycle likely facilitates multiple donor–acceptor roles in the molecular recognition process, enhancing binding enthalpy and reducing entropic penalties. This balance makes Compound 24 the most favorable ligand in terms of binding strength, pose stability, and pharmacophore potential.

Summary and Conclusion

The study evaluated thirty dioxabicyclo[3.2.1] octane-based ligands as potential SGLT2 inhibitors using molecular docking. Inspired by the clinically proven scaffold of ertugliflozin, structurally diverse analogs were designed by incorporating fused rings and heteroatoms to enhance binding interactions. Docking analysis showed that Compound 24 exhibited the strongest affinity (−10.3 kcal/mol) with excellent pose stability (RMSD 0.000 Å), followed by Compounds 25, 26, and 23. Modifications involving nitrogen- and sulfur-containing fused heterocycles significantly improved electronic and hydrophobic interactions. Overall, the findings identify Compound 24 as a promising lead for further optimization and biological evaluation.

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