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# COMPARATIVE DOCKING ANALYSIS REVEALS DIVERGENT SGLT2 SELECTIVITY, FAVORING DAPAGLIFLOZIN

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## ABSTRACT

**Background:** Sodium-glucose cotransporter 2 (SGLT2) inhibitors are widely used in type 2 diabetes therapy, but selectivity over SGLT1 is critical to minimize gastrointestinal side effects. **Objectives:** To evaluate and compare the selectivity of SGLT inhibitors, especially Dapagliflozin and Empagliflozin, toward SGLT1 and SGLT2 through molecular docking to inform future inhibitor design. **Methods:** This study used molecular docking to compare the binding profiles of five SGLT inhibitors, Dapagliflozin, Empagliflozin, Canagliflozin, Sotagliflozin, and LX2761, against SGLT1 and SGLT2 transporters **Results:** Dapagliflozin was the only compound to show statistically significant selectivity for SGLT2 over SGLT1 ($p = 0.036$), while Empagliflozin and others lacked significant differences in isoform affinity. Although Empagliflozin exhibited slightly stronger nominal binding energy to SGLT2 than Dapagliflozin, ligand efficiency (LE) analysis indicated that this was primarily due to its larger molecular size, affirming Dapagliflozin's more efficient binding. Interaction analysis further revealed that Dapagliflozin formed a clean, stabilizing pose within the SGLT2 pocket, free of repulsive interactions, unlike Empagliflozin, which displayed an unfavorable donor-donor contact in the same site. **Conclusion:** These findings support the structural basis for Dapagliflozin's higher selectivity and reinforce its profile as a SGLT2-specific agent.



## INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have become a mainstay in the treatment of type 2 diabetes mellitus and have demonstrated additional benefits in heart failure and chronic kidney disease.[1,2] These drugs act primarily by inhibiting SGLT2 in the renal proximal tubule, thereby reducing glucose reabsorption. However, some agents also inhibit SGLT1, a related transporter expressed in the intestine and other tissues. While dual SGLT1/2 inhibition may offer certain advantages, off-target SGLT1 activity has been linked to gastrointestinal side effects and may complicate the pharmacological profile.[3] Therefore, high selectivity toward SGLT2 is generally preferred for maximizing therapeutic benefit while minimizing adverse effects.

Among the approved SGLT2 inhibitors, Dapagliflozin and Empagliflozin are often compared due to their similar clinical indications and pharmacokinetic profiles. However, debate persists regarding their relative selectivity and binding efficiency to SGLT2 versus SGLT1. Some reports have suggested that Empagliflozin may offer superior SGLT2 selectivity,[4] whereas other studies indicate comparable efficacy between the two agents.[5] Despite abundant clinical data, few studies have evaluated the structural determinants of their selectivity at the molecular level. Elucidating these differences could help clarify their pharmacodynamic behavior and guide future drug design.

This study employed molecular docking and binding interaction analysis to compare the selectivity profiles of Dapagliflozin and Empagliflozin. Five SGLT inhibitors: Dapagliflozin, Empagliflozin, Canagliflozin, and Sotagliflozin, were docked against both SGLT1 and SGLT2 transporters, where LX2761

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was only docked to SGLT1. Interaction patterns, binding energies, and statistically significant differences were evaluated to determine the structural basis of isoform selectivity. LX2761 was not docked to SGLT2 due to its SGLT1 affinity and its inability to pass digestive tract. This approach aims to clarify the molecular determinants underlying Dapagliflozin and Empagliflozin selectivity for SGLT2 versus SGLT1 and contribute to the optimization of next-generation SGLT2 inhibitors.

## METHODS

### Molecular Docking and Binding Pocket Analysis

The Human Sodium-Glucose Cotransporter-1 (SGLT1) (PDB ID: 7WMV), and Sodium-Glucose Cotransporter-2 (SGLT2) (PDB ID: 7VSI) protein was retrieved from RCSB PDB as targets. SGLT1 contained LX2761 (an SGLT1 inhibitor) as bound ligand, meanwhile SGLT2 contained Empagliflozin (an SGLT2 inhibitor) as bound ligand. The method followed established protocols with modifications.[6,7] Non-standard residues (HETATM) and water molecules (HOH) were removed from the protein using Discovery Studio v25.1.0. Polar hydrogens and Kollman charges were added using AutoDock Tools v1.5.7, and the structure was saved in PDBQT format for docking.

The ligands selected, Dapagliflozin, Empagliflozin, Canagliflozin, and Sotagliflozin, were chosen based on their global clinical relevance, availability in Indonesia, and representation of either selective or dual SGLT1/SGLT2 inhibition mechanisms. Its structures were retrieved from the PubChem database in 3D SDF format. Each ligand underwent hydrogen addition and Clean Geometry using Discovery Studio v25.1.0, followed by conversion to PDB format.[8] Ligands were imported into AutoDock Tools v1.5.7, where Gasteiger charges were assigned automatically. Root detection, torsion flexibility, and aromaticity (set at a 7.5° threshold) were configured before saving the ligands in PDBQT format.[9]

The grid box was constructed by estimating the ligand's XYZ coordinates using the xyz = cmd.get coords ('selection_name', 1) command in PyMOL v3.1.3.1, with center coordinates set to x = 38, y = 51, and z = 45, and dimensions set to 40 × 40 × 40 points along each axis. Molecular docking was performed using AutoDock 4.2, employing the Genetic Algorithm for conformational search and the Lamarckian Genetic Algorithm (LGA) for scoring. Docking interactions were analyzed and visualized for the best docking pose using Discovery Studio v25.1.0.

### Statistical Analysis

Student's t-test was used to compare binding affinities between 3 top poses from each of the Gliflozins. Statistical analysis was performed in Microsoft Excel. A significance threshold (α) of 0.05 was applied to determine statistically meaningful differences in docking scores.

### Ligand Efficiency (LE) Calculation

To account for differences in ligand size, Ligand Efficiency (LE) was calculated for each compound as the ratio of docking-derived binding affinity to the number of heavy (non-hydrogen) atoms in the molecule. LE was computed using the equation[16]:

$$LE = -\frac{\Delta G}{NHA}$$

Where −ΔG is the mean binding energy (kcal/mol) from docking and NHA is the number of heavy atoms obtained from the ligand's molecular formula. Lipophilic ligand efficiency (LLE) was not considered in this analysis, as the compounds studied are approved drugs with comparable physicochemical profiles and well-established pharmacokinetic properties.

### Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Prediction

The physicochemical and pharmacokinetic properties of Dapagliflozin (Dapa) and Empagliflozin (Empa) were predicted using the SwissADME online tool[17] (https://www.swissadme.ch/). The canonical SMILES of each compound were used as input to compute molecular descriptors, including molecular weight (MW), topological polar surface area (TPSA), number of hydrogen bond donors and acceptors, rotatable bonds, lipophilicity (LogP), solubility (LogS), and molar refractivity (MR). Drug-likeness and pharmacokinetic parameters were evaluated according to Lipinski, Ghose, Veber, Egan, and Muegge rules, while additional predictions covered GI absorption, blood–brain barrier (BBB) permeability, P-glycoprotein (Pgp) substrate status, and CYP450 enzyme inhibition. All data were automatically generated and compiled for comparative analysis.

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The potential toxicological profiles of Dapagliflozin and Empagliflozin were predicted using the ProTox-3 web server[18] (https://tox.charite.de/protox3/). The canonical SMILES of each compound were submitted as input to generate in silico predictions of acute oral toxicity ($LD_{50}$ and toxicity class), organ-specific toxicity (hepatotoxicity and nephrotoxicity), and toxicological target interactions. The model integrates molecular similarity, pharmacophore modeling, fragment propensities, and machine learning algorithms trained on experimental toxicity data. Probability scores were recorded to indicate the likelihood of each toxicity endpoint, and predictions were interpreted according to the ProTox-3 toxicity classification system (classes 1–6, with class 6 representing the lowest toxicity). All results were compared and discussed in relation to each compound's pharmacological mechanism and previously predicted ADME properties.

## RESULTS

### Molecular Docking

Molecular docking of five SGLT2 inhibitors against SGLT1 and SGLT2 revealed varying binding affinities (Fig 1). Canagliflozin exhibited the strongest binding to SGLT1 (–11.09 ± 0.24 kcal/mol), followed by Sotagliflozin (–10.56 ± 0.67 kcal/mol), Empagliflozin (–9.92 ± 0.25 kcal/mol), LX2761 (–9.80 ± 0.46 kcal/mol), and Dapagliflozin (–9.42 ± 0.08 kcal/mol). Against SGLT2, Canagliflozin remained among the strongest binders (–10.86 ± 0.01 kcal/mol), along with Empagliflozin (–10.43 ± 0.40 kcal/mol), Sotagliflozin (–10.25 ± 0.30 kcal/mol), and Dapagliflozin (–9.78 ± 0.18 kcal/mol). Only Dapagliflozin and Empagliflozin showed higher binding affinity towards SGLT2 than SGLT1 receptor.

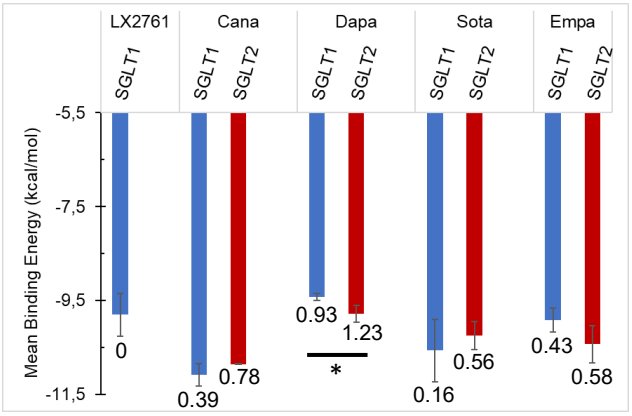


**Figure 1.** Docking energy of the Gliflozins with SGLT1 (blue) and SGLT2 (red), where y-axis represents mean binding energy (kcal/mol). T-test was used to compare each molecule's binding energy towards SGLT2 vs SGLT1 (n = 3; α = 0.05) Significant difference is marked with (*). Error bars represent deviation standard. Average RMSD is shown at the tip of each bar. Mean RMSD < 1.5 Å means a stable, well-converged pose. LX2761 was only docked to SGLT1 because it is not designed for absorption in the intestine, thus won't reach SGLT2 receptor.

Statistical comparison revealed that only Dapagliflozin showed a significant difference in binding energy between SGLT2 and SGLT1 ($p = 0.036$), with stronger binding to SGLT2. For the other compounds, the differences in binding affinities between SGLT1 and 2 were not statistically significant: Canagliflozin ($p = 0.167$), Empagliflozin ($p = 0.131$), and Sotagliflozin ($p = 0.499$). Despite the higher nominal binding energy of Empagliflozin for SGLT2, the difference was not statistically significant compared to Dapagliflozin ($p = 0.062$), suggesting similar overall affinity.

### Ligand Efficiency (LE) Calculation

In order to objectively compare the binding energy across ligands, ligand efficiency values were calculated to compare their binding affinity normalized to molecular size (Table 1). Canagliflozin exhibited an LE of 0.35 kcal/mol per heavy atom (31 heavy atoms), Dapagliflozin exhibited an LE of 0.35 kcal/mol per heavy atom (28 heavy atoms), Sotagliflozin exhibited an LE of 0.37 kcal/mol per heavy atom (28 heavy atoms), and Empagliflozin had an LE of 0.34 kcal/mol per heavy atom (31 heavy atoms).

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**Table 1**. Ligand Efficiency Value of Dapagliflozin and Empagliflozin against SGLT2 Receptor

| Ligand | Mean Binding Energy (kcal/mol) | Heavy Atom Count | LE Value |
|---|---|---|---|
| **Canagliflozin** | -10.86 | 31 | 0.35 |
| **Dapagliflozin** | -9.78 | 28 | 0.35 |
| **Sotagliflozin** | -10.25 | 28 | 0.37 |
| **Empagliflozin** | -10.43 | 31 | 0.34 |

## Binding Pocket Analysis

Molecular interaction analysis revealed that Dapagliflozin formed several stabilizing contacts within the SGLT2 binding pocket, including four conventional hydrogen bonds with PHE98, TRP291, ASN75, and HIS80 (Figure 2B). Additional interactions included π–π stacking with HIS80, a π-anion interaction with GLU99, and hydrophobic contacts involving VAL95, LEU84, and PHE453. Notably, no unfavorable interactions (e.g. donor-donor contact) were detected in this complex. In contrast, the Dapagliflozin–SGLT1 complex, although forming five hydrogen bonds (GLN457, THR287, TRP291, ASN78, HIS83), also presented one unfavorable donor–donor interaction involving LYS321. In this interaction, two hydrogen bond donors are too close to each other, causing repulsion instead of forming stabilizing H-bonds. It further exhibited π–π stacking with PHE101, a π–cation interaction with HIS83, and hydrophobic interactions with ILE98, PHE453 and LEU87 (Fig 2A).

Empagliflozin showed a comparable number and type of interactions with both SGLT isoforms (Fig 2C, 2D). In the SGLT1 complex, it formed four hydrogen bonds with ASN78, TRP291, THR287, and GLY86, accompanied by π–π T-shaped interactions with HIS83 and PHE453, and π–alkyl contacts with ILE98, ILE456, LYS157, and ALA160. No unfavorable interactions were observed in this complex. In the SGLT2 complex, Empagliflozin engaged in hydrogen bonding with GLN457, SER287, ASN75, and THR87, along with a π–cation interaction with HIS80, π–π stacking with PHE453, and π–alkyl contacts with VAL95, VAL157, LEU84, and PHE98. However, this complex included one unfavorable donor–donor interaction involving TRP291. The presence of this repulsive contact contrasts with the more uniformly stabilizing profile observed in the SGLT1 complex.

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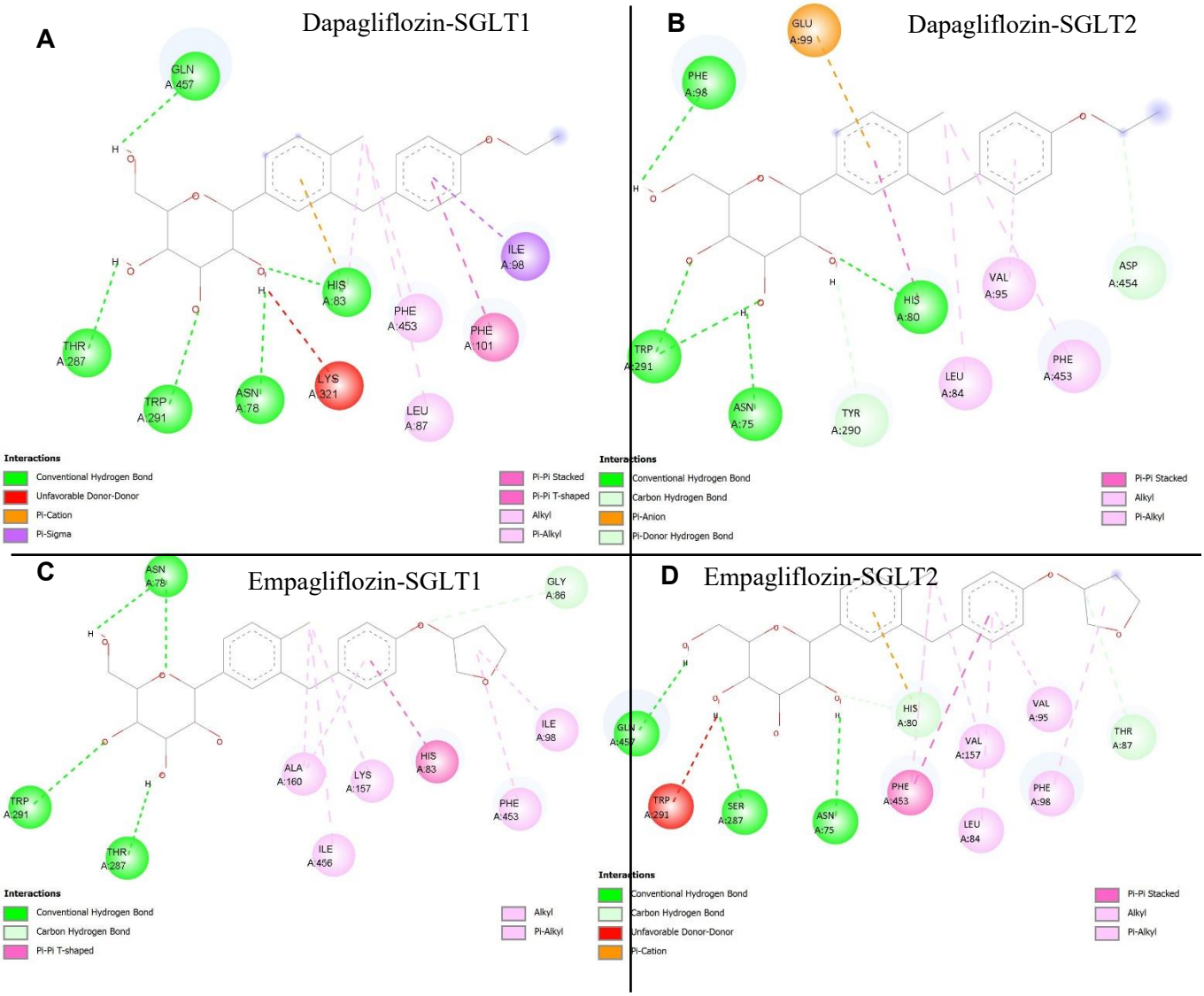


**Figure 2.** Binding Pocket Interaction of (A) Dapagliflozin-SGLT1; (B) Dapagliflozin-SGLT2; (C) Empagliflozin-SGLT1; (D) Empagliflozin-SGLT2. Visualization of docking interaction was generated using Discovery Studio v25.1.0.

## Key Residue Interaction

Residue-level comparison of the Dapagliflozin and Empagliflozin–SGLT2 complexes identified both shared and distinct anchoring patterns (Table 2). Both ligands interacted with core residues ASN75, HIS80, PHE453, and VAL95, suggesting a conserved binding region within the SGLT2 pocket. Dapagliflozin additionally engaged TRP291, TYR290, ASP454, and GLU99, residues not involved in Empagliflozin binding, through a broader range of hydrogen bonding and π-based interactions. In contrast, Empagliflozin uniquely formed interactions with GLN457, SER287, THR87, and VAL157. Despite some overlap, the ligands showed divergent residue preferences and anchor sets.

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**Table 2.** Key Residue Interactions of Dapagliflozin and Empagliflozin against the SGLT2 Receptor

| Residue | Position | Dapagliflozin Interaction | Empagliflozin Interaction |
|---|---|---|---|
| **PHE** | 98 | Conventional H-bond | Pi-Alkyl |
| **TRP** | 291 | Conventional H-bond | Unfavorable Donor–Donor |
| **ASN** | 75 | Conventional H-bond | Conventional H-Bond |
| **HIS** | 80 | Conventional H-bond & Pi–Pi Stacked | Carbon H-Bond & Pi–Cation |
| **PHE** | 453 | Pi-Alkyl | Pi–Pi Stacked & Pi-Alkyl |
| **VAL** | 95 | Pi-Alkyl | Pi-Alkyl |
| **LEU** | 84 | Alkyl | Pi-Alkyl |
| **TYR** | 290 | Non-conventional H-bond | - |
| **ASP** | 454 | Non-conventional H-bond | - |
| **GLU** | 99 | Pi–Anion | - |
| **GLN** | 457 | - | Conventional H-Bond |
| **SER** | 287 | - | Conventional H-Bond |
| **THR** | 87 | - | Carbon H-Bond |
| **VAL** | 157 | - | Pi-Alkyl |

## Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Prediction

SwissADME predictions revealed that both Dapagliflozin and Empagliflozin complied with major drug-likeness rules, showing no PAINS or Brenk alerts. Dapagliflozin exhibited a slightly lower molecular weight (408.87 g/mol) and TPSA (99.38 Å²) compared to Empagliflozin (450.91 g/mol; 108.61 Å²), indicating higher lipophilicity and better membrane permeability. Both compounds demonstrated high predicted gastrointestinal absorption and non-permeability across the BBB. The consensus LogP values (2.17 for Dapa and 1.97 for Empa) suggested moderate hydrophobicity, consistent with oral bioavailability. Both molecules were predicted as Pgp substrates and CYP2D6 inhibitors, while showing no inhibition of other CYP isoforms. Solubility predictions classified both as soluble to moderately soluble, confirming acceptable balance between hydrophilicity and lipophilicity.

Toxicity profiles of Dapagliflozin and Empagliflozin were evaluated using the ProTox-3 web server based on canonical SMILES input. Both compounds were predicted to have an oral $LD_{50}$ of 3000 mg/kg, corresponding to toxicity class 5, which indicates low acute toxicity. The models yielded average chemical similarity scores of approximately 56–57% and prediction accuracy values of 67.38%, suggesting moderate confidence in the predictions. Both molecules were predicted to be non-hepatotoxic (probabilities of 0.73 for Dapagliflozin and 0.75 for Empagliflozin) but potentially nephrotoxic (0.93 and 0.89, respectively). The predicted nephrotoxicity likely reflects their renal mechanism of action as SGLT2 inhibitors, which act directly in the proximal renal tubules to promote glucose excretion, rather than indicating direct nephron toxicity. The model isn't saying dapagliflozin or empagliflozin *kill nephrons*. It's saying their structure resembles compounds that can affect kidney cells, which makes sense given their renal mechanism of action. No interactions were detected with any of the screened toxicity-related protein targets (AA2AR, ADRB2, ANDR, AOFA, CRFR1, DRD3, ESR1, ESR2, GCR, HRH1, NR1I2, OPRK, OPRM, PDE4D, PGH1, and PRGR). Key ADMET parameters are presented in Figure 3, and the complete parameters in Table 3.

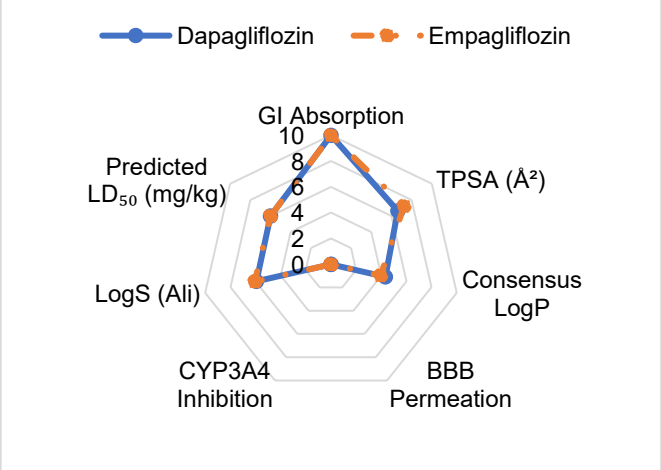


**Figure 3**. Key ADMET profiles of Dapagliflozin (blue line) and Empagliflozin (orange line) Visualized as a Radar Plot. Values were normalized (divided by max value, times 10) to allow direct comparison.

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**Table 3.** ADMET Profile of Dapagliflozin and Empagliflozin.

| Molecule | MW | TPSA | Consensus Log P | ESOL Log S | ESOL Class | Ali Log S | Ali Class | Silicos-IT LogSw | Silicos-IT class |
|---|---|---|---|---|---|---|---|---|---|
| Dapa | 408.87 | 99.38 | 2.17 | -3.78 | Soluble | -4.08 | Moderately soluble | -4.46 | Moderately soluble |
| Empa | 450.91 | 108.61 | 1.97 | -3.8 | Soluble | -3.94 | Soluble | -4.25 | Moderately soluble |

| Molecule | GI absorption | BBB permeant | Pgp substrate | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|---|---|---|---|---|---|---|---|---|
| Dapa | High | No | Yes | No | No | No | Yes | No |
| Empa | High | No | Yes | No | No | No | Yes | No |

| Molecule | Lipinski #violations | Ghose #violations | Veber #violations | Egan #violations | Muegge #violations | Bioavailability Score | PAINS #alerts | Brenk #alerts | Leadlikeness #violations |
|---|---|---|---|---|---|---|---|---|---|
| Dapa | 0 | 0 | 0 | 0 | 0 | 0.55 | 0 | 0 | 1 |
| Empa | 0 | 0 | 0 | 0 | 0 | 0.55 | 0 | 0 | 1 |

| Molecule | Predicted LD50 (mg/kg) | Predicted toxicity class | Average similarity (%) | Prediction accuracy (%) | Hepatotoxicity | Nephrotoxicity | Toxicity targets (AA2AR, ADRB2, ANDR, AOFA, CRFR1, DRD3, ESR1, ESR2, GCR, HRH1, NR1I2, OPRK, OPRM, PDE4D, PGH1, PRGR) |
|---|---|---|---|---|---|---|---|
| Dapa | 3000 | 5 | 56.77 | 67.38 | Inactive 0.73 | Active 0.93 | All black |
| Empa | 3000 | 5 | 56.9 | 67.38 | Inactive 0.75 | Active 0.89 | All black |

## DISCUSSION

The mean RMSD values provided an immediate measure of pose convergence alongside the averaged ΔG[15]. In our dataset, all of the Gliflozin's mean RMSD was low and tightly distributed, indicating a converged, well-defined binding geometry in the SGLT pockets. This strengthens confidence that the reported ΔG reflect a consistent binding mode rather than a few artifactual outliers. Thus, they are directly comparable.

The Dapagliflozin demonstrated a statistically significant preference for SGLT2 over SGLT1 ($p = 0.036$), highlighting its selective binding profile. In contrast, Empagliflozin, despite its relatively strong binding energy to SGLT2, showed no significant difference between its affinity for the two isoforms ($p = 0.131$), suggesting a broader interaction pattern. Canagliflozin and Sotagliflozin exhibited consistently high binding energies across both transporters without statistically significant difference in binding energies between their SGLT1 and SGLT2 receptors.

Only Dapagliflozin and Empagliflozin showed nominally higher binding affinity towards SGLT2 than SGLT1, with statistical significance observed only for Dapagliflozin. This specificity aligns with the results of landmark clinical trials, such as DECLARE-TIMI 58 and EMPA-REG OUTCOME, which reported cardiovascular and renal benefits alongside favorable safety profiles[2,10]. Canagliflozin and Sotagliflozin, on the other hand, exhibited higher binding affinity toward SGLT1, potentially explaining their association with increased gastrointestinal adverse events, as previously reported[11].

Despite Empagliflozin's higher nominal binding energy in the SGLT2 complex, the difference with Dapagliflozin was not statistically significant ($p = 0.062$). Ligand efficiency (LE) analysis provided critical clarification[16], showing that Dapagliflozin's slightly higher LE value made its binding more efficient relative to its molecular size. This suggests that Empagliflozin's nominal advantage in binding energy may be size-driven and not functionally meaningful. While all gliflozins tested showed favorable LE profiles, only Dapagliflozin and Empagliflozin were selected for deeper structural analysis due to their higher affinity toward SGLT2 compared to SGLT1.

The interaction profile of Dapagliflozin supports its selectivity. In the SGLT2 complex, it formed four conventional hydrogen bonds, along with hydrophobic and π-based interactions. No unfavorable interactions

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were observed. Conversely, the Dapa–SGLT1 complex, despite forming one additional hydrogen bond, exhibited a destabilizing donor–donor clash with LYS321. This contrast suggests that interaction quality, particularly the absence of repulsive contacts, contributes more meaningfully to selectivity than bond count alone. Similar conclusions were drawn in a previous structure-based analyses[12], reinforcing Dapagliflozin's structural compatibility with the SGLT2 pocket.

Empagliflozin presented similar interaction profiles with both SGLT1 and SGLT2. Hydrogen bonding and hydrophobic contacts were comparable between the two complexes, with only subtle differences in residue participation. However, the presence of an unfavorable donor–donor interaction involving TRP291 in the Empa–SGLT2 complex likely weakened its binding potential, neutralizing any interaction advantage. In contrast, the Empa–SGLT1 complex contained no such repulsive interaction, resulting in non-selective binding, a pharmacological profile less desirable for minimizing off-target SGLT1 engagement.

The residue-level interaction analysis revealed that both Dapagliflozin and Empagliflozin shared contacts with core residues such as PHE 98, TRP 291, ASN 75, HIS 80, PHE 453, VAL 95, LEU 84, in line with a previous study on SGLT2 – ligand interactions[13]. Dapagliflozin's interaction with TRP291 via a conventional hydrogen bond rather than unfavorable contact like in Empagliflozin, suggests a more stabilized and selective anchoring within the SGLT2 binding pocket.

The ADMET outputs, contextualize the docking results within likely pharmacokinetic and safety boundaries[17, 18]. Both dapagliflozin and empagliflozin satisfy major drug-likeness filters and show high predicted GI absorption, supporting the biological plausibility that differences in transporter engagement observed in silico could be pharmacologically relevant in vivo. The slightly lower MW and TPSA of dapagliflozin are consistent with the good membrane permeability[14] and may facilitate productive access to the renal SGLT2 microenvironment.

In summary, molecular docking and ligand efficiency analyses revealed that Dapagliflozin exhibits significantly greater selectivity for SGLT2 over SGLT1, both statistically and structurally. Its binding pose within the SGLT2 pocket was stabilized by multiple favorable hydrogen bonds and hydrophobic interactions, and notably free from repulsive contacts, unlike its SGLT1 counterpart or Empagliflozin's SGLT2 complex. While Empagliflozin showed comparable overall affinity, its lack of statistically significant selectivity and the presence of unfavorable interactions in the SGLT2 binding site reduce its structural favorability. The in silico ADMET profile modestly supports dapagliflozin's selective SGLT2 behavior. Dapagliflozin is smaller and has a lower TPSA, with a slightly higher consensus LogP. These differences point to marginally better passive membrane permeability and reduced polar surface[19] that can help a compact ligand reach and engage the renal SGLT2 microenvironment efficiently. These findings support the preferential use of Dapagliflozin in selective SGLT2 inhibition strategies[20] and offer molecular insight that may inform the development of next-generation inhibitors.

## CONCLUSION

Dapagliflozin showed statistically significant and structurally efficient selectivity for SGLT2, unlike Empagliflozin which exhibited non-selective binding with unfavorable contacts. Concordant in-silico ADMET pharmacokinetically supports Dapagliflozin's selective profile. These computational findings warrant follow-up with short explicit-solvent MD/MM-GBSA rescoring and targeted in vitro SGLT1/SGLT2 uptake assays to validate and translate the residue-level hypotheses.

## STUDY LIMITATIONS

This study relies on single-conformation docking, which overlooks SGLT conformational flexibility, the native binding environment, and may overestimate confidence in nominal ΔG values despite the RMSD annotations. AutoDock scoring is empirical, so absolute energies should be interpreted cautiously and would benefit from rescoring (MM-GBSA) or short explicit-solvent MD to test whether reported clashes persist and to evaluate pose stability. ADMET and toxicity outputs are in silico predictions that indicate

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plausibility but cannot substitute for experimental pharmacokinetic or toxicity assays.

## ETHICAL APPROVAL

There is no ethical approval needed.

## CONFLICTS OF INTEREST

There is no conflict of interest related to materials and publication in this study.

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## AUTHOR CONTRIBUTIONS

IDAPD designed the research concept, performed the molecular docking, ADMET, and conducted the data analysis. NLPKF contributed to reviewing the results and writing the manuscript. MP assisted in proofreading and refining the final version of the manuscript. All authors read and approved the final manuscript.

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