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ORIGINAL STUDY

Structure-Based Repurposing of Clinically Approved Compounds for PDE-5 Inhibition: Integrative Computational and Pharmacokinetic Evaluation

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ABSTRACT

Background: Phosphodiesterase-5 (PDE-5) regulates intracellular cyclic guanosine monophosphate (cGMP) levels, modulating vascular smooth muscle tone. Sildenafil, a well-established PDE-5 inhibitor, is effective for erectile dysfunction and pulmonary hypertension but causes dose-dependent adverse effects. Identifying alternative scaffolds with comparable efficacy and improved safety remains a pharmacological priority.

Methods: A ligand-based virtual screening of the DrugBank database was performed using sildenafil as a reference. Compounds exhibiting ≥60% structural and electrostatic similarity were docked into the PDE-5 catalytic domain (PDB ID: 2h42) using Glide XP in the Schrödinger Suite. Top-scoring ligands were assessed for physicochemical, pharmacokinetic (ADMET), and toxicity parameters using SwissADME and ProTox-II tools.

Results: Twenty-four FDA-approved drugs showed ≥60% similarity to sildenafil. Sildenafil exhibited the strongest binding affinity (–11.399 kcal/mol), followed by topotecan (–9.537 kcal/mol) and irinotecan (–8.542 kcal/mol). Both camptothecin derivatives formed hydrogen bonds and π–π stacking with key PDE-5 residues (Gln817, Ser663, Phe820). ADMET predictions indicated high gastrointestinal absorption and moderate oral bioavailability (0.55) for all compounds. Toxicity modeling classified sildenafil as low-risk (LD_{50} = 1000 mg/kg) and topotecan/irinotecan as moderately toxic, consistent with their anticancer pharmacology.

Conclusion: Topotecan and irinotecan demonstrated strong PDE-5 binding and favorable pharmacokinetic profiles, identifying them as promising scaffolds for selective PDE-5 inhibitor development. Despite moderate toxicity, structural optimization could improve safety, highlighting the value of *in-silico* repurposing in accelerating discovery of novel PDE-5-targeted therapeutics.

Keywords: Phosphodiesterase-5, Sildenafil, Molecular docking, Drug repurposing, ADMET, Topotecan, Irinotecan

1. Introduction

Phosphodiesterases (PDEs) are a large family of enzymes responsible for hydrolyzing cyclic nucleotides such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), key second messengers that regulate multiple physiological processes, including vascular tone, platelet aggregation, and neural signaling [1]. Among these, phosphodiesterase-5 (PDE-5) selectively degrades cGMP in smooth muscle cells, making it a critical target for conditions associated with endothelial dysfunction, including pulmonary arterial hypertension and erectile dysfunction [2].

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Sildenafil, a well-established PDE-5 inhibitor, exerts its pharmacological effect by stabilizing intracellular cGMP concentrations, resulting in nitric oxide-mediated vasodilation [2]. Despite its efficacy, sildenafil and other PDE-5 inhibitors, such as tadalafil and vardenafil, are associated with dose-related adverse effects, including headache, flushing, visual disturbances, and potential cardiovascular contraindications [3]. These limitations highlight the need to identify alternative scaffolds capable of inhibiting PDE-5 with improved selectivity, pharmacokinetics, and safety.

Drug repurposing, identifying new therapeutic uses for existing approved drugs, has emerged as a powerful strategy for accelerating drug discovery while reducing development costs and risks [4]. Computational approaches, including molecular similarity screening, docking, and ADMET prediction, have proven effective for uncovering off-target interactions and repurposing opportunities [5]. Structural and electrostatic similarity to a known inhibitor often predicts comparable binding affinity and biological activity, providing a rational framework for virtual screening and lead optimization [6]. In this context, the present study utilized a comprehensive *in-silico* workflow to identify potential PDE-5 inhibitors from the DrugBank database based on their structural similarity to sildenafil. The most promising candidates were further evaluated through molecular docking, physicochemical profiling, pharmacokinetic prediction, and toxicity assessment using advanced computational tools within the Schrödinger Suite. The study aims to identify novel, safe, and pharmacologically favorable scaffolds that could serve as leads for developing next-generation PDE-5 inhibitors or alternative therapeutics targeting cGMP-regulated pathways.

2. Materials and methods

Computational tools used for this study were built into the Schrödinger Suite software (version 14.4, 2025-2).

2.1. Ligand library generation

Sildenafil, a standard drug that inhibits the activity of phosphodiesterase, was used to screen a ligand library for compounds similar in shape (electroshape) and chemistry. Evidently, compounds with electrostatic potentials similar to Sildenafil are more likely to interact with phosphodiesterase comparably. This similarity can lead to effective inhibition of the enzyme, thereby increasing phosphate levels. Furthermore, molecules with shapes similar to Sildenafil can fit into the phosphodiesterase active site more snugly, enhancing their inhibitory potential. This shape complementarity ensures that the molecules can occupy the same spatial region as Sildenafil, facilitating similar interactions. Twenty-four test compounds, with a similarity index $>$ 60% were identified using the DrugBank database (Table 1). A $\geq$60% 3D structural/electrostatic similarity threshold was selected because similarity values above 0.6 are widely recognized in ligand-based virtual screening as the minimum range that reliably preserves pharmacophoric alignment and binding-site complementarity with the reference ligand [7, 8]. The compounds' structure data file (SDF) format was retrieved for further analysis.

2.2. Protein preparation

The crystal structure of phosphodiesterase-5 (PDE-5) in complex with Sildenafil (PDB ID: 2h42) was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org). The protein was prepared using the Protein Preparation Wizard in Maestro (Schrödinger Suite), which involved the addition of missing hydrogen atoms, assignment of bond orders, and optimization of hydrogen bonding networks. Water molecules beyond 5 Åfrom the active site were removed, and restrained energy minimization was performed using the OPLS4 force field to relieve steric clashes while maintaining the experimental geometry.

2.3. Ligand preparation

The 24 FDA-approved small molecules retrieved from the DrugBank database and Sildenafil were prepared using LigPrep (within the Schrödinger Suite) to generate 3D conformations, assign correct ionization states at physiological pH (7.0 $\pm$ 0.2) using Epik, and minimize geometries with the OPLS4 force field. Stereoisomers and tautomers were generated where applicable to ensure proper sampling during docking.

2.4. Receptor grid generation

The receptor grid was generated using Glide Receptor Grid Generation, centered on the co-crystallized ligand binding site. The grid box dimensions were set to adequately encompass the PDE-5 catalytic pocket, ensuring coverage of key binding residues such as Gln817, Phe820, and Ser815. Van der Waals scaling of 1.0 and a partial charge cutoff of 0.25 were applied to soften nonpolar ligand–receptor interactions.

2.5. Molecular docking protocol

Prepared ligands were docked into the PDE-5 receptor grid using Glide XP (Extra Precision) flexible ligand sampling mode. This method incorporates stringent scoring functions, enhanced sampling, and detailed evaluation of hydrophobic enclosure, hydrogen bonding, and π–π stacking interactions. The docking output was ranked by GlideScore (kcal/mol), where more negative values indicate stronger predicted binding affinity.

2.6. Drug-likeness evaluation

The drug-likeness of the best three compounds was assessed using SwissADME (http://www.swissadme.ch), an online tool that predicts pharmacokinetic properties and drug-likeness based on molecular descriptors [9]. Drug-likeness was evaluated using Lipinski's Rule of Five, which stipulates acceptable thresholds for molecular weight (<500 Da), lipophilicity (LogP <5), hydrogen bond donors (<5), and hydrogen bond acceptors (<10).

2.7. Toxicity risk assessment

The safety profile of the two compounds and the native ligand were evaluated using ProTox-II (https://tox.charite.de/protox3), a web-based platform that predicts various toxicity endpoints, including LD_{50}, hepatotoxicity, carcinogenicity, immunotoxicity, and mutagenicity, using machine-learning models trained on experimental data [10].

3. Results

3.1. Similarity screening of DrugBank compounds

Twenty-four FDA-approved compounds were identified from the DrugBank database based on structural and electrostatic similarity to sildenafil (DB00203), which served as the reference compound with a similarity score of 1.00 (Table 1). Pafolacianine, Cobamamide, Hydroxocobalamin, and Mecobalamin showed the highest resemblance (0.643–0.654), indicating strong potential for comparable PDE-5 inhibition. Several anticancer agents, including Irinotecan, Topotecan, and Vinblastine, exhibited moderate similarity (0.630–0.637), while Reserpine and Deserpidine showed the lowest values (~0.603).

Table 1. Similarity scores of FDA-approved compounds relative to Sildenafil.

DrugBank ID	Screened Drug	Similarity Score
DB00203	Sildenafil	1.00
DB15413	Pafolacianine	0.654
DB11191S	Cobamamide	0.650
DB00200	Hydroxocobalamin	0.646
DB03614	Mecobalamin	0.643
BD15444	Elexacaftor	0.638
DB00762	Irinotecan	0.637
DB11641	Vinflunine	0.635
DB00570	Vinblastine	0.632
DB01030	Topotecan	0.631
DB00541	Vincristine	0.630
DB00309	Vindesine	0.628
DB12674	Lurbinectedin	0.628
DB00361	Vinorelbine	0.637
DB01220	Rifaximin	0.623
DB00615	Rifabutin	0.620
DB15673	Lenacapavir	0.620
DB11613	Velpatasvir	0.611
DB00115	Cyanocobalamin	0.609
DB06290	Simeprevir	0.605
DB01201	Rifapentine	0.604
DB01045	Rifampin	0.603
DB05109	Trabectedin	0.603
DB00206	Reserpine	0.603
DB01089	Deserpidine	0.602

Table 2. Glide XP docking scores for PDE-5 and screened ligands.

DrugBank ID	Generic Name	No. of Valid XP Poses	Docking Score (kcal/mol)
DB00203	Sildenafil	2	–11.399
DB01030	Topotecan	3	–9.537
DB00762	Irinotecan	1	–8.542
DB15673	Lenacapavir	1	–7.200
DB01089	Deserpidine	3	–7.126
DB06290	Simeprevir	1	–6.648
DB00206	Reserpine	1	–5.557
DB15444	Elexacaftor	1	–4.908

3.2. Molecular docking scores

Molecular docking of the screened ligands against the PDE-5 catalytic domain revealed varying binding affinities; the best docking scores are shown in Table 2. Only eight ligands successfully generated valid docked poses, while the remaining compounds failed to produce acceptable conformations under the XP scoring constraints. This may be attributable to XP penalties (e.g., steric clashes, improper hydrophobic enclosure, or unfavourable electrostatic orientation). Sildenafil exhibited the strongest binding with a docking score of –11.399 kcal/mol, validating its known inhibitory potency. Topotecan (–9.537 kcal/mol) and Irinotecan (–8.542 kcal/mol) also demonstrated strong affinities, suggesting potential PDE-5 interaction. Lenacapavir, Deserpidine, and Simeprevir showed moderate binding scores (–7.2 to –6.6 kcal/mol), while Reserpine and Elexacaftor had the weakest interactions (–5.557 and –4.908 kcal/mol, respectively).

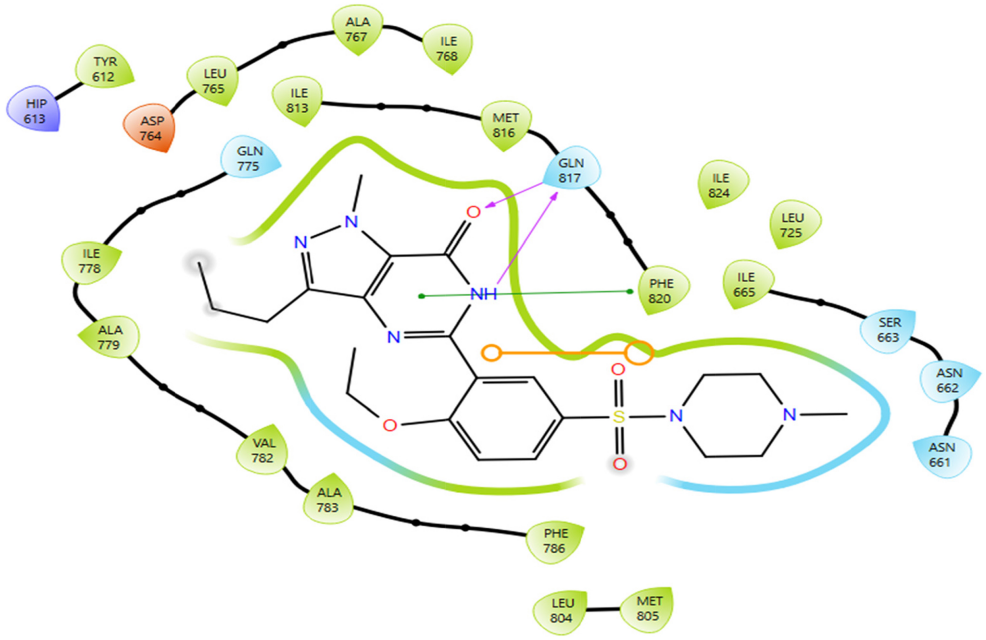

Fig. 1. Predicted binding pose of Sildenafil within the active site of PDE-5 from XP docking.

3.3. Binding interaction analysis of the top three compounds

Sildenafil exhibited the strongest binding affinity (–11.399 kcal/mol), occupying the PDE-5 catalytic pocket with its pyrazolopyrimidinone core engaging in π–π stacking interactions with Phe820 and hydrogen bonds with Gln817 and Ser663, stabilizing the scaffold within the hydrophobic cavity. The sulfonamide group formed polar interactions with residues such as Tyr612 and Ser663, while hydrophobic contacts with Leu725, Val782, and Ile665 reinforced binding (Fig. 1). These interactions align with the known PDE-5 inhibition mechanism of Sildenafil, validating the docking protocol.

Topotecan bound deeply within the PDE-5 active site (–9.537 kcal/mol), with its planar camptothecin ring system enabling π–π stacking with Phe820 and hydrogen bonding to residues Thr723 and Gln817. The lactone moiety oriented toward the polar surface, interacting with Ser815 and Met816, while hydrophobic contacts with Leu804, Val782, and Phe786 further stabilized the complex (Fig. 2). The presence of both aromatic and polar interactions suggests a potential dual anchoring mode within the PDE-5 binding pocket.

Irinotecan aligned within the PDE-5 binding pocket with its polycyclic camptothecin scaffold spanning the hydrophobic cavity and its piperidine side chain extending toward the solvent-exposed entrance. The ligand formed two hydrogen bonds, one between the hydroxyl group and Ser663, and another with Thr723, contributing to anchoring at the active site. Additionally, π–π stacking with Phe820 stabilized the aromatic chromophore, while a salt bridge with Arg667 enhanced electrostatic complementarity. Hydrophobic interactions with Ile665, Val782, Leu804, Met816, and Phe786 further stabilized the complex. The lactone moiety engaged in van der Waals contacts and oriented toward polar residues Gln817 and Ser815, providing additional stabilization. This network of hydrogen bonds, π–π stacking, and hydrophobic contacts supports Irinotecan's docking score of –8.542 kcal/mol and suggests possible PDE-5 binding compatibility (Fig. 3).

3.4. Physicochemical properties of selected compounds

Table 3 summarizes the physicochemical properties of Sildenafil, Irinotecan, and Topotecan. Sildenafil (474.58 g/mol) meets all Lipinski's criteria, while Irinotecan (586.68 g/mol) shows one violation due to its higher molecular weight. Topotecan (421.45 g/mol) is the smallest and most polar compound. The TPSA (104.89–121.80 Å^2) and molar refractivity (114.81–169.63) values indicate that all three compounds possess suitable properties for good permeability and potential oral bioavailability.

3.5. Pharmacokinetic properties of selected compounds

Table 4 presents the predicted pharmacokinetic characteristics of Sildenafil, Irinotecan, and Topotecan. All three compounds exhibit high gastrointestinal (GI) absorption but are non-permeant across

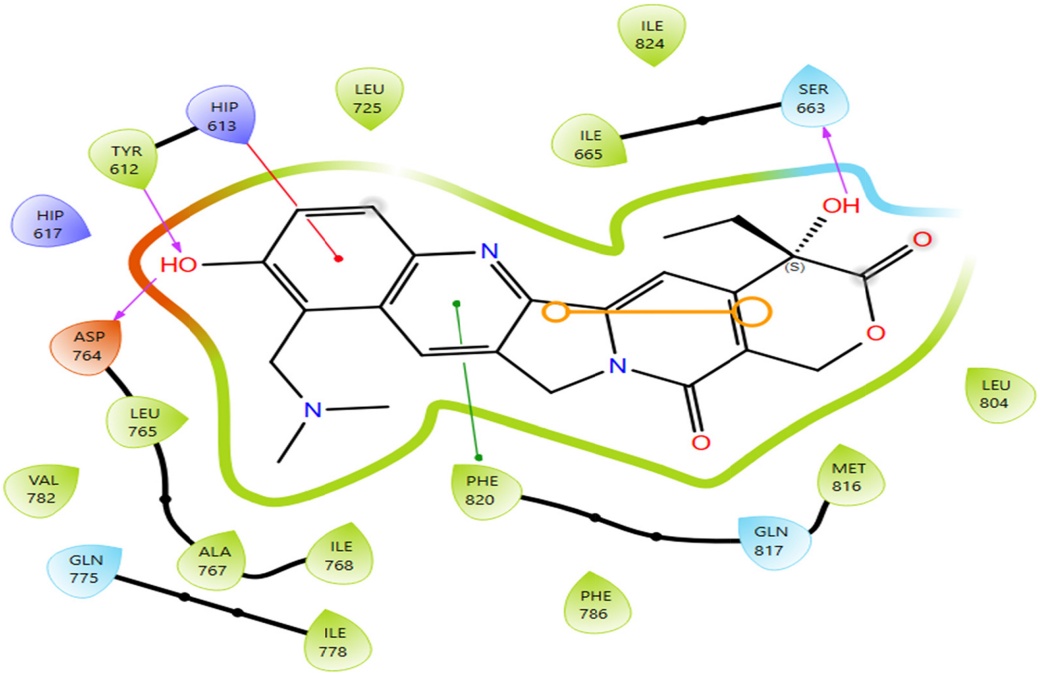

Fig. 2. Predicted binding pose of Topotecan in the PDE-5 binding site.

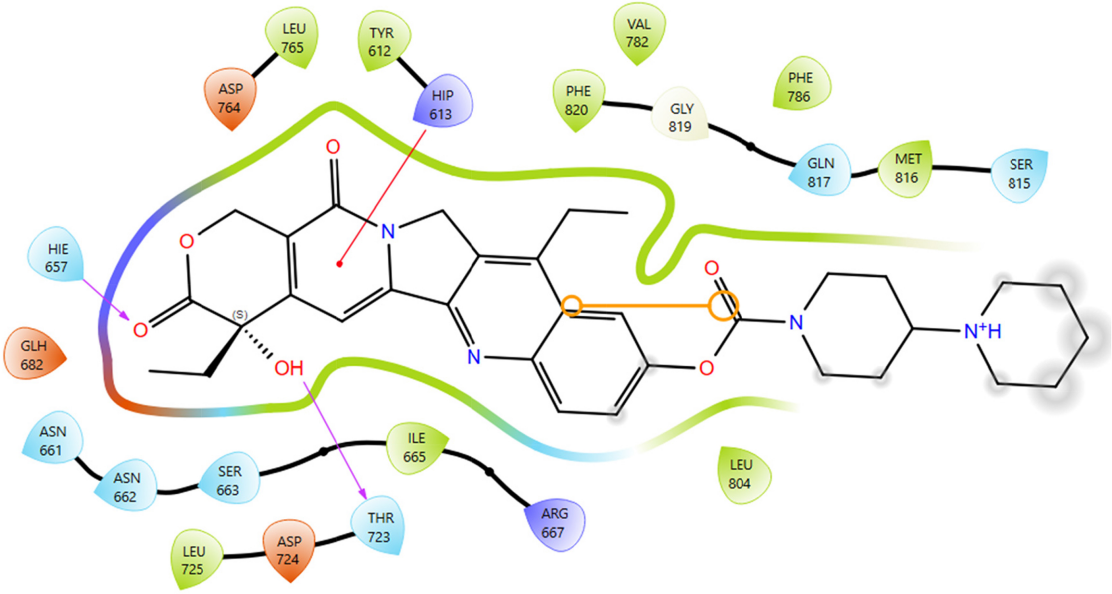

Fig. 3. Predicted binding pose of Irinotecan (DB00762) docked into PDE-5.

the blood–brain barrier (BBB). Each act as a P-glycoprotein (Pgp) substrate, suggesting active efflux potential. All compounds inhibit CYP2C9 and CYP3A4, indicating possible drug–drug interaction risks via these metabolic pathways. Irinotecan uniquely inhibits CYP2D6, while Sildenafil and Topotecan do not. The predicted skin permeability (Log Kp) ranged from –7.22 to –8.14 cm/s, consistent with low dermal absorption.

3.6. Predicted Lipophilicity of selected compounds

Table 5 shows the predicted lipophilicity (Log P) values of Sildenafil, Irinotecan, and Topotecan. Irinotecan exhibited the highest lipophilicity with a consensus Log P of 3.73, indicating greater membrane permeability and lower solubility. Sildenafil and Topotecan showed moderate lipophilicity, with consensus Log P values of 1.94 and 1.86, respectively,

Table 3. Physicochemical properties of test compounds.

Property	Sildenafil	Irinotecan	Topotecan
Molecular weight (g/mol)	474.58	586.68	421.45
Heavy atoms	33	43	31
Heavy aromatic	15	16	16
Rotatable bonds (nRot)	7	6	3
H-bond acceptors (nHA)	8	8	7
H-bond donors (nHD)	1	1	2
Molar refractivity (MR)	134.56	169.63	114.81
TPSA (Å^2)	121.80	114.20	104.89
Lipinski violations	0	1	0

Table 4. Predicted Pharmacokinetic properties of test compounds.

Parameter	Sildenafil	Irinotecan	Topotecan
GI absorption	High	High	High
BBB permeant	No	No	No
Pgp substrate	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	Yes	Yes	Yes
CYP2D6 inhibitor	No	Yes	No
CYP3A4 inhibitor	Yes	Yes	Yes
Log Kp (cm/s)	–8.14	–7.22	–8.00

Table 5. Predicted lipophilicity (Log P) values of test compounds.

Parameter	Sildenafil	Topotecan	Irinotecan
iLOGP	3.03	2.79	4.95
XLOGP3	1.48	1.22	3.74
WLOGP	1.93	1.43	3.07
MLOGP	1.20	0.98	2.55
SILICOS-IT Log P	2.06	2.88	4.33
Consensus Log P_o/w	1.94	1.86	3.73

suggesting balanced hydrophilic–lipophilic characteristics favourable for oral absorption.

The passive absorption and permeability behaviour of the selected compounds were further illustrated using the BOILED-Egg predictive model (Fig. 4). The plot represents the relationship between lipophilicity (WLOGP) and polarity (topological polar surface area, TPSA), which jointly determine the likelihood of gastrointestinal absorption and blood–brain barrier (BBB) penetration. The white region corresponds to the space of high human intestinal absorption (HIA), while the yellow region indicates the BBB permeation zone. All three compounds fell within or near the HIA region, suggesting favourable intestinal absorption. However, none of them resided within the BBB zone, indicating limited potential for central nervous system (CNS) penetration. The blue-bordered symbols represent P-glycoprotein (PGP) substrates, confirming active efflux characteristics consistent with their pharmacokinetic predictions.

3.7. Predicted water solubility and bioavailability of test compounds

Table 6 presents the predicted solubility and bioavailability profiles of Sildenafil, Irinotecan, and Topotecan. Based on ESOL and Ali models, Sildenafil and Topotecan are classified as soluble, while Irinotecan is moderately to poorly soluble, reflecting its higher lipophilicity. The predicted logS values (–3.02 to –7.28) indicate that Sildenafil (–3.59) and Topotecan (–3.41) have better aqueous solubility compared to Irinotecan (–5.71). All compounds exhibited a bioavailability score of 0.55, suggesting moderate oral absorption potential (Fig. 5).

3.8. Predicted toxicity profiles of test compounds

The predicted toxicity analysis revealed that Sildenafil had the highest LD_{50} (1000 mg/kg) and was the least toxic, while Topotecan showed the greatest toxicity (LD_{50} = 50 mg/kg, Class 5). Irinotecan exhibited moderate toxicity (Class 4). Both Irinotecan and Topotecan were associated with neurotoxicity, nephrotoxicity, immunotoxicity, and cytotoxicity, consistent with their anticancer profiles, while Sildenafil showed minimal toxicity apart from respiratory effects (Table 7).

4. Discussion

This *in silico* repurposing study explored FDA-approved compounds for potential inhibition of PDE-5, a key enzyme regulating intracellular cGMP levels. By integrating similarity screening, molecular docking, and pharmacokinetic analyses, this study identified structurally diverse candidates capable of mimicking sildenafil's electrostatic and spatial properties. Computational repurposing strategies such as this provide a rapid, cost-effective route to identify novel applications for approved drugs, significantly reducing the developmental timeline compared with de novo discovery [11]. Electroshape-based screening yielded 24 DrugBank compounds with ≥60% similarity to sildenafil, encompassing anticancer, antiviral, and vitamin derivatives. This diversity demonstrates that PDE-5's catalytic site can accommodate ligands of various scaffolds, provided they share comparable polar and aromatic features. Sildenafil exhibited the strongest binding affinity (–11.399 kcal/mol), validating the docking model and reflecting its established PDE-5 inhibitory mechanism (Corbin & Francis, 2021).

Topotecan (–9.537 kcal/mol) and irinotecan (–8.542 kcal/mol) emerged as particularly promising

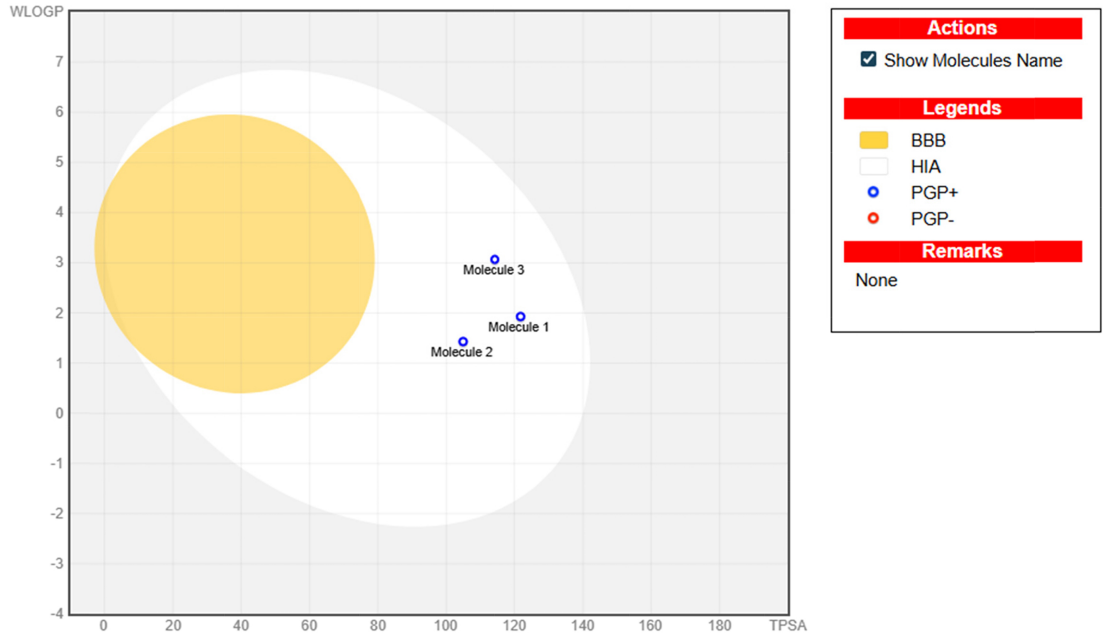

Fig. 4. BOILED-Egg model of pharmacokinetic prediction for sildenafil (molecule 1), irinotecan (molecule 2), and topotecan (molecule 3).

Table 6. Predicted water solubility (Log S) and bioavailability profiles of test compounds.

Parameter	Sildenafil	Irinotecan	Topotecan
LogS (ESOL)	–3.59	–5.71	–3.41
ESOL solubility (mg/ml)	1.22e-1	1.14e-03	1.66e-01
ESOL solubility (mol/L)	2.58e-04	1.94e-06	3.93e-04
ESOL class	Soluble	Moderately soluble	Soluble
Ali LogS	3.64	–5.83	–3.02
Ali solubility (mg/mL)	1.08e-01	8.67e-04	4.03e-01
Ali solubility (mol/L)	2.27e-04	1.48e-06	9.55e-04
Ali class	Soluble	Moderately soluble	Soluble
Silicos-IT LogSw	–5.83	–7.28	–5.71
Silicos-IT solubility (mg/mL)	7.08e-01	3.09e-05	8.26e-04
Silicos-IT solubility (mol/l)	1.89e-06	5.26e-08	1.96e-06
Silicos-IT class	Moderately soluble	Poorly soluble	Moderately soluble
Bioavailability score	0.55	0.55	0.55

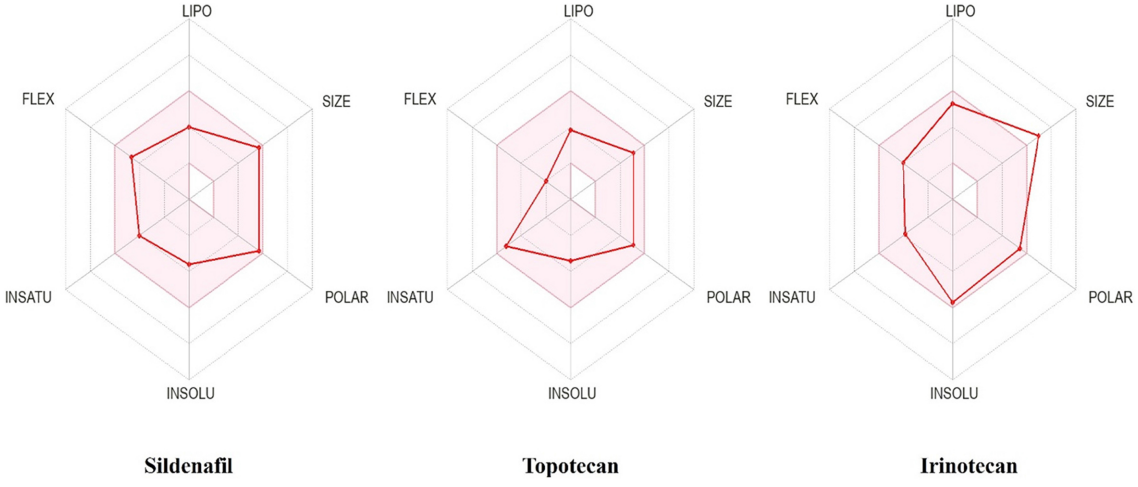

Fig. 5. Bioavailability radar of the selected compounds.

Table 7. Predicted toxicity and organ-specific effects of Sildenafil, Irinotecan, and Topotecan.

Parameters	Sildenafil	Irinotecan	Topotecan
Predicted LD50	1000 mg/kg	765 mg/kg	50 mg/kg
Predicted toxicity class	4	4	5
Hepatotoxicity	Inactive	Inactive	Inactive
Neurotoxicity	Inactive	Active	Active
Nephrotoxicity	Inactive	Active	Active
Respiratory toxicity	Active	Active	Active
Cardiotoxicity	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Active	Active
Mutagenicity	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Active	Active

repurposing candidates. Their camptothecin cores facilitated π–π stacking with Phe820 and hydrogen bonding with Gln817 and Ser663, interactions essential for cGMP binding and hydrolysis inhibition. Additional van der Waals and hydrophobic contacts with Leu804, Val782, and Phe786 stabilized the complexes, suggesting that both compounds could sterically and electrostatically complement the PDE-5 pocket [12]. These binding patterns closely resemble sildenafil's interaction map and align with the concept of "scaffold mimicry," wherein structurally distinct molecules achieve equivalent binding efficacy via convergent pharmacophore topologies [13]. Physicochemical data revealed that all three compounds exhibit favourable topological polar surface areas (<125 Å^2) and molar refractivity values, implying good passive permeability [14]. Sildenafil adhered to Lipinski's rule of five, while irinotecan marginally exceeded the molecular weight threshold (586.68 g/mol). Despite this, its high binding affinity suggests potential optimization avenues such as prodrug formation or structural truncation to restore ideal drug-likeness [15].

The ADMET profiles of sildenafil, topotecan, and irinotecan provide important insights into their suitability as potential PDE-5–targeting scaffolds. All three compounds demonstrated high gastrointestinal absorption, suggesting favourable oral uptake, which is a desirable property for lead optimization. Their non-permeability across the BBB indicates limited CNS exposure, reducing the likelihood of CNS-related adverse effects, an important safety consideration for peripheral targets such as PDE-5 [3]. The three compounds were predicted to be P-glycoprotein (P-gp) substrates, implying susceptibility to efflux transport. While this may limit intracellular accumulation, it also decreases the risk of tissue overexposure and may help mitigate toxicity, especially for structurally complex molecules. Inhibition of CYP2C9 and CYP3A4 across all candidates signals possible metabolic interactions, consistent with the clinical pharmacology of sildenafil [16]. The solubility and lipophilicity data further distinguish the compounds. Sildenafil and topotecan displayed moderate lipophilicity (Log P $\approx$1.8–1.9) and were classified as soluble on multiple prediction models, supporting efficient absorption and favourable distribution. In contrast, irinotecan exhibited higher lipophilicity (Log P $\approx$ 3.7) and markedly lower aqueous solubility, which may limit its oral bioavailability without structural modification. Nevertheless, its strong PDE-5 binding affinity suggests that rational derivatization could optimize both potency and solubility. All compounds shared a bioavailability score of 0.55, indicative of moderate oral absorption. These results illustrate the delicate equilibrium between solubility and membrane permeability, a critical determinant of pharmacokinetic success [17].

The toxicity predictions were consistent with known pharmacological profiles. Sildenafil showed the highest LD_{50} (1000 mg/kg) and minimal organ toxicity, confirming its favourable safety margin. In contrast, irinotecan and topotecan, both cytotoxic anticancer agents, displayed neurotoxicity, nephrotoxicity, and immunotoxicity, characteristic of their DNA-topoisomerase I inhibition mechanism; however, myelosuppression is the most common or dose-limiting side effect [18]. Importantly, none of the compounds exhibited hepatotoxicity, cardiotoxicity, or mutagenicity. This highlights the potential for structural optimization to retain PDE-5 binding affinity while mitigating systemic toxicity.

Beyond their established indications, PDE-5 inhibitors have shown promise in treating cardiovascular disorders, pulmonary hypertension, lower urinary symptoms, diabetes mellitus, and chronic kidney disease through modulation of the nitric oxide/cGMP signalling pathway [19, 20]. The identification of topotecan and irinotecan as potential PDE-5 binders suggests novel therapeutic opportunities in areas such as tumour angiogenesis inhibition, where PDE-5 blockade can suppress vascular endothelial

growth factor (VEGF)–mediated signalling. Moreover, given PDE-5's role in neuroinflammation and synaptic plasticity, these compounds could be explored for neuroprotective or anti-inflammatory indications, provided structural modifications minimize cytotoxic effects. Thus, this study not only expands the chemical landscape of PDE-5 inhibitors but also provides computational evidence supporting broader pharmacological repurposing opportunities within cardiovascular and neurological domains.

5. Conclusion

Through a comprehensive *in silico* approach, this study identified topotecan and irinotecan as high-affinity PDE-5 ligands with strong binding energies (–9.537 and –8.542 kcal/mol, respectively) and interaction networks comparable to sildenafil (–11.399 kcal/mol). Although both compounds display moderate toxicity associated with their anticancer function, their pharmacokinetic and physicochemical properties indicate potential for scaffold optimization into selective, safer PDE-5 inhibitors. The findings validate the use of computational repurposing pipelines to uncover novel biological targets for approved drugs, thereby accelerating early-stage discovery. Given that irinotecan and topotecan are clinically cytotoxic agents with narrow therapeutic windows, the camptothecin core identified in our docking analysis should be viewed as a scaffold for lead generation rather than a direct repurposing of the parent drugs. Medicinal-chemistry strategies (scaffold-hopping/bioisosteric replacement), prodrug or targeted-delivery approaches, and rigorous biochemical/cellular deconvolution are required to preserve PDE-5 engagement while abrogating topoisomerase I–mediated cytotoxicity; such strategies are well established in the literature and justify further preclinical optimisation rather than immediate clinical translation [21]. Future studies should integrate molecular dynamics simulations, enzyme inhibition assays, and cell-based pharmacological profiling to confirm PDE-5 inhibition experimentally and evaluate off-target effects. Ultimately, these efforts could facilitate the rational development of new PDE-5-targeted therapeutics for cardiovascular, neuroprotective, and anti-inflammatory indications, reinforcing the translational power of in silico drug repurposing.

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Not applicable.

Ethical statement

Not applicable.

Data availability statement

All data supporting the findings of this study are available within the manuscript.

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Conflicts of interest

The author declares that there is no conflict of interest.

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