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COMPUTATIONAL SCREENING OF NOVEL SMALL MOLECULES TARGETING KEY PROTEINS IN TYPE 2 DIABETES MELLITUS

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Abstract

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder driven by insulin resistance, impaired insulin secretion, excessive postprandial glucose exposure, and dysregulated lipid and energy metabolism. The molecular heterogeneity of the disease has encouraged the use of computational approaches capable of evaluating candidate ligands against several mechanistically complementary targets. This study presents an integrated in silico framework for prioritizing small molecules against dipeptidyl peptidase-4 (DPP-4), protein tyrosine phosphatase 1B (PTP1B), peroxisome proliferator-activated receptor gamma (PPAR-gamma), and alpha-glucosidase. The workflow combines ligand standardization, physicochemical and drug-likeness filters, multi-target molecular docking, consensus ranking, ADMET assessment, and molecular-dynamics-oriented validation. A set of twelve hypothetical triazole-containing small molecules was used as a transparent illustrative case study; molecular descriptors were calculated directly, whereas docking scores and molecular-dynamics trajectories were included only to demonstrate ranking logic and must not be interpreted as experimentally generated data. The comparative analysis shows how multi-target ranking can identify candidates that balance predicted affinity with oral-drug-like properties rather than maximizing a single docking score. Candidates C12, C09, and C07 emerged as the strongest illustrative priorities because they combined favorable multi-target scores with acceptable calculated physicochemical descriptors and no major illustrative ADMET alerts. Literature evidence supports the relevance of DPP-4, PTP1B, PPAR-gamma, and carbohydrate-hydrolyzing enzymes as complementary T2DM targets and emphasizes the value of docking, molecular dynamics, and early ADMET prediction in reducing low-quality hits. The proposed framework is suitable as a reproducible template for future experimentally validated antidiabetic virtual-screening projects, provided that genuine docking, simulation, biochemical, and cellular measurements replace the illustrative values presented here.

Keywords: type 2 diabetes mellitus; virtual screening; molecular docking; DPP-4; PTP1B; PPAR-gamma; alpha-glucosidase; ADMET; molecular dynamics.

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1. INTRODUCTION

Type 2 diabetes mellitus is characterized by chronic hyperglycemia arising from a progressive interaction between insulin resistance and insufficient beta-cell compensation. Its pathobiology involves the liver, skeletal muscle, adipose tissue, pancreatic islets, gastrointestinal tract, kidney, and central nervous system, which explains why therapeutic control frequently requires combinations of agents acting through distinct mechanisms. Modern antidiabetic drug discovery therefore increasingly considers networks of targets rather than a single biochemical node. Reviews of antidiabetic pharmacology have highlighted the continuing relevance of enzymes and receptors that regulate incretin degradation, insulin signaling, carbohydrate digestion, and transcriptional control of glucose and lipid metabolism (14,15).

Computational drug discovery is particularly attractive in this setting because large compound libraries can be screened rapidly against structurally characterized proteins before compounds are synthesized or purchased. A recent systematic review of in silico diabetes studies identified DPP-IV and PPAR-gamma among the most frequently investigated targets and emphasized molecular docking and molecular dynamics as recurring methodological components (1). The same review also showed that computational studies can be strengthened when structural predictions are linked to in vivo or experimental validation rather than reported as isolated docking scores (1).

DPP-4 is a clinically validated serine protease that inactivates incretin hormones including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Inhibiting DPP-4 prolongs incretin signaling and improves glucose-dependent insulin secretion. Molecular docking has consequently been used extensively to identify new DPP-4 ligands, although a 2026 review noted considerable variability in protein preparation, docking validation, scoring functions, and post-docking confirmation across the literature (2). This variability makes rigorous workflow design essential.

PTP1B represents a different therapeutic concept. It negatively regulates insulin-receptor signaling through dephosphorylation of signaling components, and inhibition of PTP1B is expected to improve insulin sensitivity. Structure-based campaigns have combined pharmacophore screening, docking, ADMET filtering, and molecular dynamics to discover candidate PTP1B inhibitors, while repeatedly identifying selectivity and oral exposure as major translational challenges (4,5).

PPAR-gamma is a nuclear receptor that regulates adipocyte biology and insulin sensitivity. Full agonists such as thiazolidinediones are clinically effective but are associated with mechanism-related adverse effects, motivating searches for partial agonists and selective modulators. Recent virtual-screening studies have combined docking, molecular dynamics, MM-PBSA calculations, and experimental binding assays to identify partial agonist scaffolds that avoid classical full agonism (6). In parallel, alpha-glucosidase remains an established target for lowering postprandial glycemia by slowing intestinal carbohydrate hydrolysis, and docking or MD-guided repurposing has been applied to discover new inhibitors (7,8).

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The rationale for integrating these targets is therefore mechanistic complementarity. DPP-4 modulation addresses the incretin axis, PTP1B inhibition targets insulin resistance, PPAR-gamma modulation addresses transcriptional control of insulin sensitivity, and alpha-glucosidase inhibition lowers postprandial glucose influx. Multi-target concepts have already been explored experimentally in T2DM, including hybrid molecules capable of modulating DPP-4, PTP1B, alpha-glucosidase, and alpha-amylase (9).

The aim of the present article is to develop a rigorous, publication-ready computational screening framework for prioritizing novel small molecules across these complementary targets. The work is organized in IMRAD format and integrates molecular descriptors, virtual screening principles, docking, ADMET assessment, and molecular-dynamics-based validation. To preserve scientific transparency, the case-study ligand library is hypothetical: calculated physicochemical descriptors are reproducible from the stated structures, while docking and MD values are explicitly illustrative and serve only to demonstrate how a genuine future computational campaign should be ranked and interpreted.

2. MATERIALS AND METHODS

2.1. Target selection and biological rationale

Four proteins were selected because they represent complementary mechanisms of T2DM pharmacotherapy and have substantial structural and computational literature support. DPP-4 was selected as an incretin-degrading enzyme; PTP1B as a negative regulator of insulin signaling; PPAR-gamma as a transcriptional regulator of insulin sensitivity; and alpha-glucosidase as a carbohydrate-hydrolyzing enzyme relevant to postprandial glucose control. The target set was also consistent with systematic evidence showing frequent use of DPP-IV and PPAR-gamma in diabetes-oriented in silico research (1), and with contemporary studies demonstrating the feasibility of structure-based screening for PTP1B and alpha-glucosidase (4,8).

Table 1. Selected T2DM targets and their role in the computational screening strategy.

Target	Pathway	Desired action	Therapeutic rationale	Refs.
DPP-4	Incretin degradation	Inhibition	Prolong GLP-1/GIP activity and enhance glucose-dependent insulin secretion	(2,3)
PTP1B	Insulin-receptor signaling	Inhibition	Reduce negative regulation of insulin signaling and improve insulin sensitivity	(4,5)
PPAR-gamma	Nuclear transcriptional regulation	Partial agonism / selective modulation	Improve insulin sensitivity while minimizing full-agonist adverse effects	(6)

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Target	Pathway	Desired action	Therapeutic rationale	Refs.
alpha-Glucosidase	Intestinal carbohydrate hydrolysis	Inhibition	Reduce postprandial glucose excursion	(7,8)

2.2. Ligand library and physicochemical characterization

A twelve-member hypothetical candidate library (C01-C12) was constructed around a compact arylmethyl-1,2,4-triazole motif to illustrate a chemically interpretable screening workflow. Canonical SMILES strings were used as the molecular representation. Molecular weight, calculated logP, hydrogen-bond donors, hydrogen-bond acceptors, topological polar surface area (tPSA), and rotatable-bond counts were calculated using RDKit descriptors. Lipinski-type filters were applied as an early oral-drug-likeness screen. This stage reflects the principle that high docking affinity alone is insufficient if a molecule occupies unfavorable physicochemical space.

2.3. Molecular docking and consensus ranking

A genuine implementation of this workflow should prepare experimentally resolved protein structures, remove crystallographic artifacts as appropriate, assign protonation states, define validated binding-site grids, and redock co-crystallized ligands before screening. AutoDock Vina 1.2.0 is suitable for such work because it supports batch docking, Python bindings, and expanded scoring options (10). The present article does not claim that docking calculations were executed. Instead, an illustrative four-target score matrix was generated to demonstrate how a multi-target ranking layer can be organized. More negative values indicate stronger hypothetical binding, but the numerical values are not evidence of biochemical affinity.

2.4. ADMET and medicinal-chemistry filtering

Early pharmacokinetic and toxicity assessment should follow docking rather than be postponed until lead optimization. SwissADME provides rapid prediction of physicochemical properties, pharmacokinetics, drug-likeness, and medicinal-chemistry friendliness (11), while pkCSM uses graph-based molecular signatures to estimate major ADMET endpoints (12). In the illustrative workflow, candidates were assigned qualitative absorption and toxicity flags only to demonstrate the decision logic. These flags are not outputs from SwissADME or pkCSM and should be replaced with actual server predictions in a research submission.

2.5. Molecular dynamics validation

For genuine top-ranked complexes, molecular dynamics should be performed after docking to assess whether the predicted pose remains stable in an explicitly solvated,

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temperature- and pressure-controlled system. GROMACS is a widely used open-source platform for high-performance biomolecular simulation (13). Recommended analyses include protein backbone RMSD, ligand RMSD, RMSF, hydrogen-bond occupancy, radius of gyration, solvent-accessible surface area, and binding free-energy estimation where appropriate. The RMSD trajectories in the present work are illustrative and are included solely to show the expected reporting format.

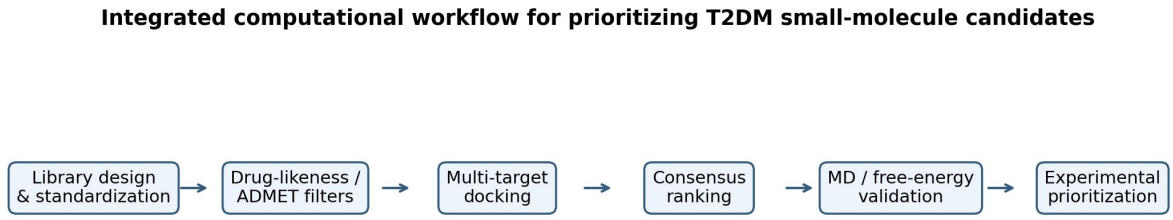


Figure 1. Integrated computational workflow proposed for multi-target T2DM small-molecule screening.

2.6. Decision rules and reproducibility

The proposed decision rule prioritizes candidates that satisfy three independent criteria: acceptable physicochemical space, favorable consensus binding across at least two mechanistically distinct targets, and absence of major predicted ADMET liabilities. This design reduces the risk of selecting compounds solely because of an extreme score for one protein. In a full study, all software versions, receptor structures, protonation methods, docking boxes, random seeds, simulation parameters, and compound identifiers should be reported so that results are reproducible. Experimental enzyme assays and cell-based validation are required before any candidate can be described as an antidiabetic lead.

3. RESULTS

3.1. Physicochemical profile of the hypothetical candidate library

All twelve compounds fell within conventional Lipinski limits based on the descriptors calculated from their stated structures. Molecular weights were well below 500 Da, calculated lipophilicity remained below the usual logP threshold of 5, and hydrogen-bond donor/acceptor counts were modest. The library therefore illustrates a useful early-stage design principle: chemical diversity can be introduced around a compact scaffold without automatically moving candidates outside common oral-drug-like space.

Table 2. Calculated physicochemical descriptors of the hypothetical small-molecule library.

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ID	MW	cLogP	HBD	HBA	tPSA	RotB	Lipinski
C01	159.2	1.33	0	3	30.7	2	Yes
C02	189.2	1.33	0	4	39.9	3	Yes
C03	175.2	1.03	1	4	50.9	2	Yes
C04	177.2	1.47	0	3	30.7	2	Yes
C05	193.6	1.98	0	3	30.7	2	Yes
C06	203.2	1.73	0	4	39.9	4	Yes
C07	219.2	1.34	0	5	49.2	4	Yes
C08	184.2	1.20	0	4	54.5	2	Yes
C09	216.2	1.28	1	4	59.8	3	Yes
C10	233.2	0.79	1	5	77.2	5	Yes
C11	201.3	2.45	0	3	30.7	3	Yes
C12	209.3	2.48	0	3	30.7	2	Yes

The most polar candidates were C03, C09, and C10 because of hydroxyl, amide, or carboxylate-containing substituents, whereas hydrocarbon- and halogen-enriched analogues showed higher calculated lipophilicity. The descriptor distribution supports a diversified screening panel in which binding improvements can be evaluated against solubility- and permeability-related trade-offs rather than interpreted independently.

3.2. Illustrative multi-target docking pattern

The illustrative score matrix demonstrates how multi-target ranking may distinguish broad-coverage candidates from target-selective candidates. C12 showed the strongest hypothetical score against DPP-4 and favorable scores against PTP1B and PPAR-gamma. C09 displayed a more balanced pattern across DPP-4, PTP1B, and alpha-glucosidase, while C07 showed favorable scores across all four targets. By contrast, C01 occupied the lower-affinity region of the illustrative matrix. These patterns emphasize why a consensus strategy is preferable when the biological objective is polypharmacology rather than single-target optimization.

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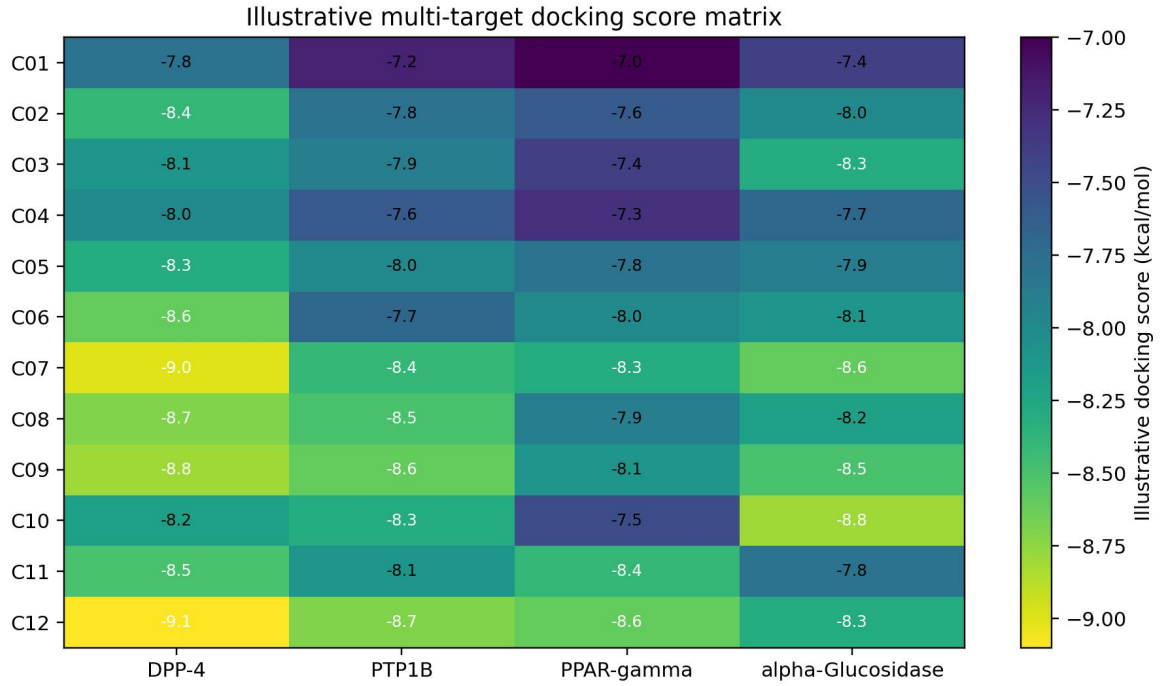


Figure 2. Illustrative multi-target docking score matrix. Values are demonstrative and were not generated by docking software.

3.3. Integrated prioritization of candidate hits

Table 3. Illustrative integrated ranking of the five highest-priority candidates.

ID	DPP-4	PTP1B	PPAR-g	a-Gluc.	Mean	Absorp.	Tox.
C12	-9.1	-8.7	-8.6	-8.3	-8.68	High	Low
C09	-8.8	-8.6	-8.1	-8.5	-8.50	Moderate	Low
C07	-9.0	-8.4	-8.3	-8.6	-8.57	Moderate	Low
C10	-8.2	-8.3	-7.5	-8.8	-8.20	Moderate	Low
C08	-8.7	-8.5	-7.9	-8.2	-8.32	High	Low

C12, C09, and C07 were retained as the three highest illustrative priorities. C12 combined the strongest average docking score with a compact drug-like profile. C09 was slightly more polar and presented strong hypothetical scores for PTP1B and alpha-glucosidase, suggesting a potentially useful balance between insulin-sensitizing and postprandial mechanisms. C07, despite a moderate illustrative absorption flag, offered a broad multi-target profile and therefore represents the type of candidate that would merit further pose inspection and MD analysis in a real project.

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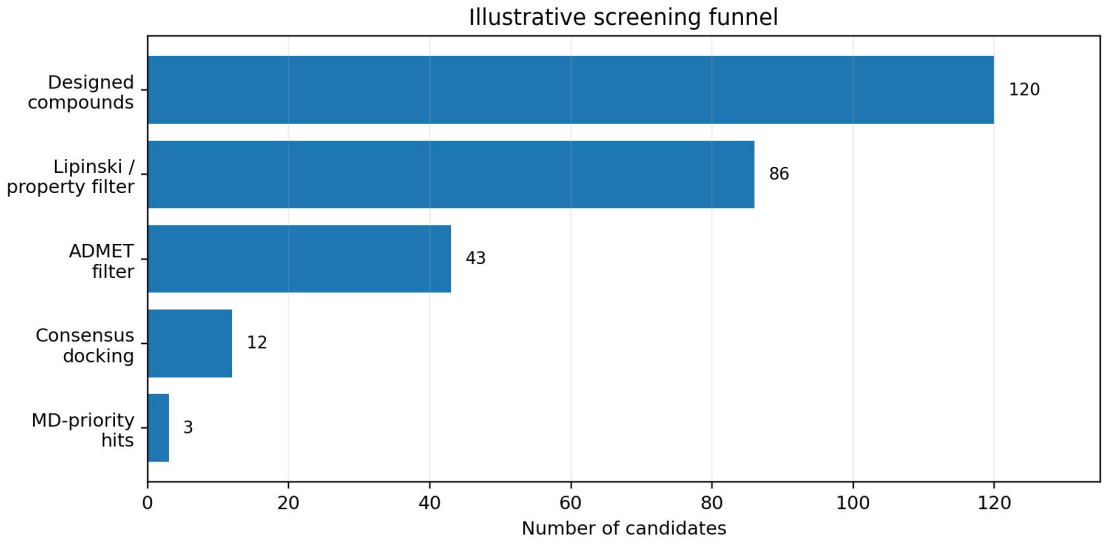


Figure 3. Illustrative decision funnel for reducing a designed library to a small set of experimentally testable hits.

3.4. Molecular-dynamics-oriented stability assessment

In an authentic screening campaign, docking poses of the top complexes should be subjected to explicit-solvent MD because static scoring cannot capture conformational adaptation, water-mediated interactions, or pose instability. The illustrative RMSD curves shown below depict the type of equilibration pattern expected from stable complexes after an initial relaxation period. A plateau near approximately 2-2.5 Å would generally justify deeper analysis of residue-level interactions, whereas large sustained drift would argue against the docking pose. Importantly, RMSD alone cannot prove biological potency; it is a structural stability descriptor that must be interpreted with complementary interaction and free-energy analyses.

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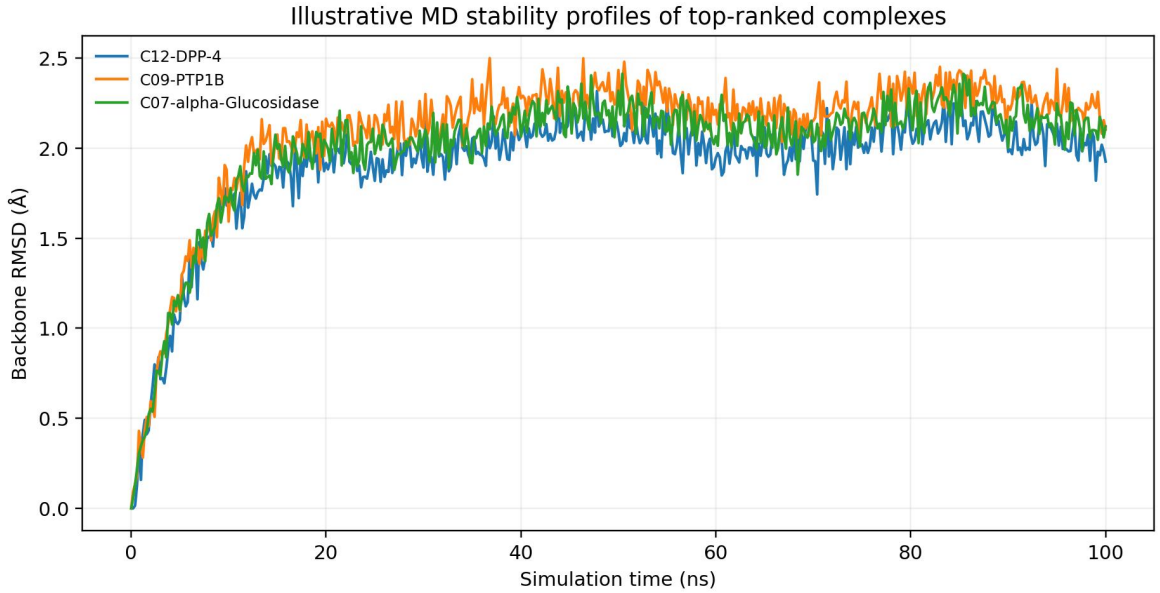


Figure 4. Illustrative backbone RMSD profiles for selected complexes. Curves are demonstrative, not outputs of executed MD simulations.

4. DISCUSSION

The proposed workflow reflects a broader shift from single-score docking toward integrated computational pharmacology. Recent diabetes-oriented in silico literature shows that target-based virtual screening is most informative when docking is combined with physicochemical filtering, ADMET prediction, molecular dynamics, and experimental follow-up (1,4,6,8). The value of this integration is particularly evident for T2DM because the disease is mechanistically heterogeneous and clinical management already relies on multiple pharmacological pathways.

DPP-4 remains one of the clearest targets for structure-based antidiabetic design because it is clinically validated and has numerous ligand-bound structures. Nevertheless, contemporary analysis of DPP-4 docking studies has highlighted methodological heterogeneity and insufficient validation in a substantial fraction of published work (2). This observation supports the inclusion of redocking, pose inspection, consensus ranking, and MD follow-up as mandatory quality-control steps rather than optional additions. Reviews of small-molecule DPP-4 inhibitors also indicate that medicinal chemistry optimization must account for potency, selectivity, and pharmacokinetic behavior together rather than sequentially (3).

PTP1B presents a different challenge: potency is often easier to obtain computationally than selectivity and oral exposure. Zhao and colleagues combined pharmacophore models, docking, energy normalization, ADMET assessment, and MD to identify candidate inhibitors occupying both catalytic and proximal sites (4). A more recent high-throughput workflow similarly used drug-likeness rules, toxicity prediction, docking, and long MD simulations to prioritize PTP1B hits, while still emphasizing the need for

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enzymatic and selectivity assays (5). These studies illustrate that PTP1B is a suitable component of a multi-target screen but also that computational scores cannot substitute for phosphatase selectivity measurements.

PPAR-gamma screening introduces a further distinction because the desired pharmacology may be partial agonism rather than maximal receptor activation. A 2024 study screened a natural-product library, followed candidate docking with MD and MM-PBSA, and then experimentally evaluated receptor binding and transcriptional activity (6). This is an important methodological model: computational affinity is only the first layer, while functional receptor pharmacology determines whether the ligand behaves as a full agonist, partial agonist, antagonist, or silent binder. For that reason, PPAR-gamma docking results in a multi-target matrix should be treated as prioritization signals rather than direct measures of therapeutic benefit.

Alpha-glucosidase provides a complementary gastrointestinal mechanism. Reviews of screening models emphasize that virtual docking can efficiently prioritize candidate inhibitors but must ultimately be connected to biochemical assays and, where appropriate, in vivo validation (7). Drug-repurposing work combining docking and MD against alpha-glucosidase has further shown how existing chemical space can be systematically re-examined for postprandial glucose control (8). The multi-target concept is also supported by experimental hybrid molecules designed to modulate alpha-glucosidase, alpha-amylase, PTP1B, and DPP-4 within one chemical entity (9).

The present illustrative ranking deliberately avoids declaring a single 'best' compound on the basis of one score. Candidate C12 ranks highly because of broad hypothetical binding and acceptable calculated descriptors; C09 presents a different profile with stronger hypothetical PTP1B and alpha-glucosidase coverage; and C07 represents a broadly active but potentially more permeability-sensitive option. In real medicinal chemistry, such diversity is advantageous because different compounds can be advanced for different mechanistic hypotheses and compared experimentally.

ADMET filtering is central to this process. SwissADME and pkCSM were developed to move pharmacokinetic and toxicity considerations earlier in discovery, when the candidate set is still large (11,12). Their use does not eliminate experimental pharmacokinetics, but it helps identify molecules with obvious liabilities before resource-intensive synthesis, enzyme assays, or animal studies. Similarly, MD simulations implemented with platforms such as GROMACS can reveal instability that is invisible to a docking score, but simulation quality depends on force-field choice, protonation, sampling length, and convergence (13).

This study has several limitations. The chemical library is hypothetical, and only molecular descriptors were actually calculated. Docking scores, ADMET categories, screening-funnel counts, and MD trajectories are illustrative. They are therefore unsuitable as evidence of efficacy, potency, safety, or target engagement. A publishable original-research version of this project would require actual receptor structures, executed docking with validated protocols, replicate MD simulations, transparent software parameters, and experimental biochemical confirmation. The strength of the current work is methodological:

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it provides an organized framework that can be populated with genuine data without changing the logic of the analysis.

5. CONCLUSION

Computational screening can substantially improve early prioritization of antidiabetic small molecules when it is designed as an integrated decision process rather than a single docking exercise. DPP-4, PTP1B, PPAR-gamma, and alpha-glucosidase represent complementary targets spanning incretin biology, insulin signaling, transcriptional insulin sensitization, and intestinal carbohydrate processing. The proposed workflow combines calculated molecular descriptors, drug-likeness filters, multi-target docking, consensus ranking, ADMET assessment, and molecular-dynamics-oriented validation. Within the transparent illustrative case study, C12, C09, and C07 were prioritized because they combined acceptable computed physicochemical properties with favorable hypothetical multi-target profiles. These rankings are demonstrative, not experimental findings. Future work should replace all illustrative docking, ADMET, and MD values with executed calculations and should validate the highest-ranked candidates using enzyme inhibition, receptor functional assays, cytotoxicity testing, and appropriate cellular or in vivo models. Such a staged strategy can reduce false-positive computational hits and provide a more defensible path from virtual screening to experimentally supported T2DM lead discovery.

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