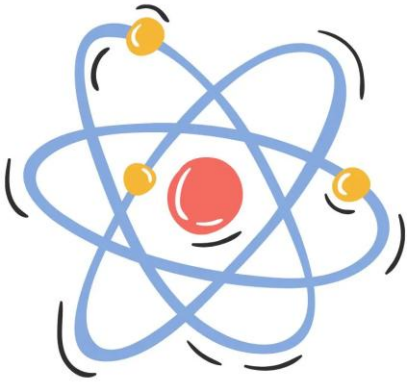

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ABSTRACT: *Peroxisome proliferator-activated receptor gamma (PPAR-γ) remains one of the most extensively pursued nuclear receptor targets in the treatment of type 2 diabetes mellitus, metabolic syndrome, and, increasingly, inflammatory and oncological disease. Decades of thiazolidinedione-based drug development established proof of therapeutic concept but simultaneously exposed the mechanistic liabilities of full agonism at this receptor, most notably fluid retention, weight gain, and cardiovascular risk arising from complete stabilization of helix 12 and constitutive coactivator recruitment. The emergence of two complementary computational paradigms is now reshaping how medicinal chemists approach this target. Graph neural networks (GNNs), which represent small molecules as attributed molecular graphs rather than fixed-length descriptor vectors, have demonstrated superior performance in virtual screening, binding-affinity prediction, and pharmacokinetic property estimation across diverse drug targets. In parallel, core-hopping and scaffold-hopping methodologies allow medicinal chemists to replace a validated pharmacophoric core with topologically distinct but electronically and geometrically compatible alternatives, offering a route to novel intellectual property, improved selectivity, and mitigated toxicity liabilities without discarding validated structure-activity knowledge. This review synthesizes the structural biology of the PPAR-γ ligand-binding domain, surveys classical structure-based design campaigns undertaken against this receptor and critically examines the architectures and applications of GNNs in contemporary virtual screening. We then propose an integrated GNN-guided virtual screening and core-hopping workflow tailored specifically to PPAR-γ modulator design, built around the goal of identifying selective partial agonists and biased ligands that retain insulin-sensitizing efficacy while minimizing helix-12-driven adverse transcriptional programs. Design considerations including selectivity across the PPAR α/β/δ/γ subfamily, avoidance of Ser273 phosphorylation, trans repression-biased anti-inflammatory signalling, and generative-model-assisted lead optimization are discussed in a tabulated, comparative format intended as a practical reference for computational and medicinal chemists developing next-generation PPAR-γ therapeutics.*

KEYWORDS: *PPAR-γ; graph neural networks; virtual screening; scaffold hopping; core hopping; molecular docking; molecular dynamics; selective PPAR-γ modulators; de novo drug design; type 2 diabetes*

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1. Introduction: Classical Structure-Based Approaches To PPAR-γ Ligand Design

Prior to the widespread adoption of deep learning, PPAR-γ drug discovery relied predominantly on molecular docking, pharmacophore modeling, and molecular dynamics (MD)/MM-GBSA free-energy estimation anchored to available crystal structures (commonly PDB entries such as 2PRG, 1FM9, 3B0R, and 2P4Y). Natural-product-focused virtual screening campaigns identified flavonoid derivatives of kaempferol, quercetin, and resveratrol as PPAR-γ binders, with MD/MM-GBSA analysis over tens of nanoseconds confirming stable hydrogen bonding and favorable free energies relative to reference ligands [16]. Comparative molecular field analysis (CoMFA)-based 3D-QSAR combined with docking and MD has similarly guided the design of dual PPAR-α/γ agonists intended to treat combined dyslipidemia and type 2 diabetes without the isoform-selective liabilities of single-target TZDs [17]. Structurally diverse chemotypes coumarin-chalcone hybrids [18], indoline/natural-product-derived scaffolds [19], and benzothiazole-based PPAR-δ-selective agonists identified via proprietary docking-based virtual screening [20] collectively demonstrate that the AF-2 pocket tolerates considerable scaffold diversity provided the core hydrogen-bond anchor to Ser289/His323/His449/Tyr473 is preserved.

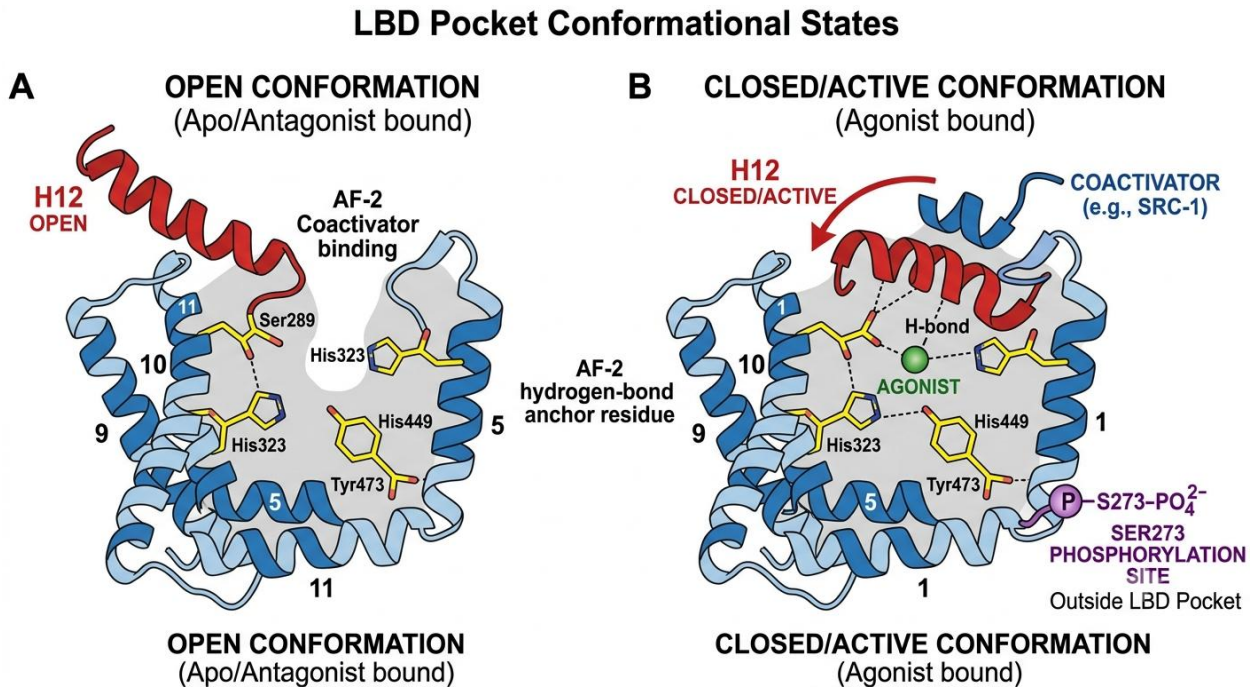

Figure 1: A schematic of the LBD pocket showing helix 12 in its "open" vs. "closed/active" conformation, the AF-2 hydrogen-bond anchor (Ser289, His323, His449, Tyr473), and the Ser273 phosphorylation site outside the pocket.

A second, more recent wave of classical SBDD studies has focused specifically on partial agonism. Guasch et al. combined structure-based pharmacophore construction with electrostatic/shape similarity screening

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of an 89,165-compound natural-product library to identify ten novel chemical scaffolds later confirmed as PPAR-γ partial agonists that stimulate insulin-induced glucose uptake without inducing adipogenesis [10]. Building on this partial-agonist paradigm, rationally designed thiazolidine-4-one-gallic-acid hybrid derivatives were shown by extended MD and post-MD binding-energy decomposition to form weaker H12–Tyr473 hydrogen bonds than the rosiglitazone co-crystal, consistent with a partial rather than full agonist profile [11]. Fragment-based drug design combined with pharmacophore-guided virtual screening has likewise produced TZD analogues (e.g., SP4e/SP4f) with docking and MM/GBSA-predicted affinities comparable to or exceeding pioglitazone, later confirmed in vivo in rodent models of diabetes [21,22]. Phytochemical screening campaigns from Abrus seed extracts [23] to ferulic-acid derivatives [24] and the lignan phillyrin identified through combined network pharmacology and MD/MM-GBSA [25] extend this structure-based paradigm to natural-product chemical space and underscore the persistent medicinal chemistry interest in non-TZD, non-adipogenic PPAR-γ ligands.

Table1. Representative classical structure-based design studies on PPAR-γ and related PPAR isoforms

Ligand Class	Computational Method	Key Structural Finding	Ref.
Kaempferol/quercetin/ resveratrol derivatives	Docking + MD + MM-GBSA	Demethyltorosaflavone D shows highest binding stability; quercetin derivative dominates ΔG contribution	[16]
PPAR-α/γ dual agonist series	3D-QSAR (CoMFA) + docking + MD	CoMFA contour maps guided design of stable dual-isoform binders	[17]
Coumarin-chalcone fibrates	Docking + SAR	Electron-withdrawing C6′ substituent increases PPAR-α/γ efficacy	[18]
Natural-product-derived dual agonists	Structure- and ligand-based virtual screening	Ten leads upregulate ABCA1/ABCG1 cholesterol transporters	[19]
Benzothiazole PPAR-δ agonists	Proprietary docking-based virtual screening	Compound 12 shows high PPAR-δ potency/selectivity and in vivo efficacy	[20]
Natural-product partial agonists	Pharmacophore + docking + shape/electrostatic similarity	135 candidates from 89,165 compounds; 5 confirmed partial agonists in vitro	[10]
Thiazolidine-4-one–gallic acid hybrids	Docking + MD + post-MD ΔG decomposition	Weaker Tyr473 H-bonding than rosiglitazone consistent with partial agonism	[11]
Fragment-grown thiazolidine-2,4-diones	Fragment-based design + docking + MM/GBSA	SP4e/SP4f show ΔG comparable to pioglitazone; confirmed hypoglycemic in vivo	[21,22]
Abrus precatorius phytochemicals	ADMET screening + docking + MM/GBSA + MD	Chlorogenic acid and quercetin outperform acarbose reference	[23]

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Ferulic acid derivatives	SBDD + DFT + docking + MD	Ser342/Arg280 anchor hydrogen bonds; stable 50 ns trajectories	[24]
Phillyrin (lignan)	Network pharmacology + docking + MD/MM-GBSA	Validated experimentally as a PPAR-γ ligand improving insulin resistance	[25]

2. Graph Neural Networks in Virtual Screening

Graph neural networks encode a molecule as a graph G = (V, E) in which atoms are nodes bearing feature vectors (element, hybridization, formal charge, aromaticity) and bonds are edges bearing their own feature vectors (bond order, conjugation, ring membership). Message-passing layers iteratively update each node's representation by aggregating information from neighbouring nodes and edges, after which a readout (pooling) function produces a fixed-length embedding of the entire molecule for downstream regression or classification. This paradigm used in graph convolutional networks (GCN), graph attention networks (GAT), message-passing neural networks (MPNN), and graph isomorphism networks (GIN) has repeatedly outperformed fingerprint-based machine learning (random forest, SVM, gradient boosting) and simple feed-forward QSAR models on benchmark virtual screening tasks, because it learns task-relevant substructural patterns directly from data rather than relying on hand-engineered descriptors.

Recent literature illustrates the breadth of GNN application relevant to a PPAR-γ campaign. Hybrid graph-transformer/CNN-BiLSTM architectures such as GraphTransDTI combine graph-structural drug encoding with protein sequence context via cross-attention to predict drug-protein interaction strength, achieving competitive performance even in cold-start (unseen drug or unseen target) scenarios relevant to novel-scaffold prioritization [28]. Multimodal frameworks that fuse quantum-derived three-dimensional electron-density descriptors with graph convolutional drug-disease association models have shown measurable AUC gains (approximately 9%) over conventional ECFP4 fingerprint baselines by incorporating genuinely three-dimensional electronic information into the graph representation [27]. Molecular-protein fusion frameworks that jointly embed a protein language model (e.g., ESM2) with a message-passing GNN over the ligand graph have proven capable of prioritizing a small, experimentally tractable hit list (in one case, 2,663 candidates) from screening libraries exceeding 130,000 compounds against a structurally challenging oncology target, with docking and 300 ns MD subsequently used for orthogonal structural validation — a two-stage GNN-then-physics workflow directly transferable to PPAR-γ [26]. Large-language-model-augmented dual graph architectures (DualPG-DTA) that construct separate ligand and protein graphs processed through attention-equipped GNNs have identified sub-nanomolar kinase inhibitors with confirmed in vivo efficacy, illustrating that GNN-prioritized hits can proceed successfully through lead optimization to demonstrated pharmacology [29].

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GNNs are equally valuable for the frequently underappreciated task of decoy elimination prior to docking: graph convolutional classifiers trained on the DUD-E benchmark have achieved AUCs approaching 0.98 in distinguishing true small-molecule binders from property-matched decoys, substantially reducing downstream docking and MD compute burden [30]. Beyond binding-affinity classification, GNNs have been applied to frontier molecular orbital and reactivity prediction relevant to electronic-property-guided lead optimization [33], to physiologically based pharmacokinetic modelling through chemical graph convolutional networks that predict human intravenous pharmacokinetic parameters directly from structure [34], and to synergy prediction between geroprotective natural compounds acting on interconnected aging-related pathways [36] a conceptually relevant precedent for predicting synergistic or additive pharmacology between a designed PPAR-γ ligand and adjunct metabolic agents. GNN-based screening has also been extended to antibody and biologic modalities, including graph-based prediction of complementarity-determining-region conformational flexibility [37] and integrated docking/GNN/MD pipelines for antibody repurposing [35], reflecting the generality of the message-passing paradigm across small-molecule and biologic drug classes alike.

Table 2. Graph neural network architectures and representative applications relevant to PPAR-γ virtual screening

GNN Architecture	Core Mechanism	Representative Application	Ref.
Graph Convolutional Network (GCN)	Spectral/spatial neighbor-feature averaging	True-binder vs. decoy classification (DUD-E, AUC ≈ 0.98)	[30]
Graph Attention Network (GAT)	Learned attention weights over neighbor nodes	Frontier molecular orbital / reactivity prediction	[33]
Message-Passing Neural Network (MPNN)	Iterative edge-conditioned message passing	Molecular-protein fusion virtual screening (ESM2 + MPNN-GNN)	[26]
Graph Isomorphism Network (GIN)-based (GraphDTA/GINConvNet)	Sum-aggregation with high discriminative power	Drug-target affinity prediction for natural-product screening	[31]
Graph Transformer + CNN-BiLSTM hybrid	Cross-attention fusion of graph and sequence encodings	Cold-start drug-protein interaction prediction	[28]
Chemical Graph Convolutional Network (CGCNN)	Graph convolution fused with PBPK simulation	Human intravenous pharmacokinetic (AUC, Cmax) prediction	[34]
3D-CNN-assisted consensus docking	Spatial convolution over docked-pose voxel grids	TCM-derived enzyme inhibitor discovery with MM/PBSA triage	[32]
Multimodal diffusion GCN (MsDGCN)	Multi-scale diffusion over heterogeneous biological graphs	Drug-disease association with 3D electron-density fusion	[27]

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LLM-augmented dual-graph network (DualPG-DTA)	Dual ligand/protein graphs with pre-trained language embeddings	Sub-nanomolar kinase inhibitor discovery with in vivo validation	[29]

3. GNN-Guided Virtual Screening of PPAR-γ Chemical Space

Although the peer-reviewed literature applying GNNs directly to PPAR-γ remains comparatively sparse relative to oncology and infectious-disease targets, the cross-target precedents summarized in Section 4 map onto a coherent, immediately transferable workflow for this receptor. A practical GNN guided PPAR-γ campaign begins with careful curation of a labeled training set bioactivity records for the PPAR-γ target (indexed under identifiers such as ChEMBL235) spanning full agonists, partial agonists, SPPARγMs, inverse agonists, and confirmed inactives since the dual-task nature of the problem (binary active/inactive classification alongside continuous pIC50/pKi regression) benefits from multi-task GNN architectures that share early message-passing layers while branching into task-specific readout heads. Ligand featurization should encode not only two-dimensional graph topology but also, where docked or co-crystallized poses are available, three-dimensional pocket-contact information (distance to Ser289/His323/His449/Tyr473, and proximity to the H12 stabilizing cavity), since this π-pocket geometry is mechanistically decisive in distinguishing full agonists from partial agonists and inverse agonists.

Following model training and rigorous scaffold-split (rather than random-split) validation essential to avoid the optimistic bias that random splitting introduces when chemically similar analogues appear in both training and test sets the trained GNN can be deployed to rank ultra-large virtual libraries (from tens of thousands to hundreds of thousands of compounds, analogous in scale to the 130,000–170,000-compound campaigns reported for other GNN prioritized targets [26]) at a computational cost several orders of magnitude below exhaustive physics-based docking. Decoy-elimination GNN classifiers [30] can additionally be interposed as a pre-filter to remove compounds unlikely to engage the AF-2 pocket productively before committing docking and MD resources to the surviving candidates. The output of this stage is not a final hit list but a computationally enriched, mechanistically stratified shortlist compounds predicted to bind with a partial-agonist-like or Ser273 phosphorylation-blocking profile are prioritized preferentially over those predicted to behave as classical full agonists, directly operationalizing the SPPARγM design philosophy discussed in Section 2 within a high-throughput in silico framework.

Table 3. Proposed GNN-guided virtual screening workflow for PPAR-γ modulator discovery

Workflow Stage	Computational Task	Recommended Approach / Precedent
Data curation	Assemble labeled PPAR-γ bioactivity set (ChEMBL235); annotate agonist class (full/partial/SPPARγM/inverse)	Multi-source aggregation with explicit mechanistic class labels, not activity value alone

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2. Featurization	Encode 2D graph topology plus, where available, 3D pocket-contact descriptors	Node/edge features + distance-to-Ser289/His323/His449/Tyr473 and H12-cavity proximity
3. Model architecture	Multi-task GNN: shared message-passing trunk, classification + regression heads	MPNN/GIN backbone analogous to [26,28,29]
4. Validation strategy	Scaffold-split cross-validation; external temporal hold-out	Avoids inflated performance from near-duplicate analogues across splits
5. Decoy pre-filtering	GNN-based true-binder/decoy triage prior to docking	GCNN classifier analogous to DecoyFinderNetAna [30]
6. Ultra-large library screening	Rank 10^4–10^6 compounds by predicted class + affinity	Scale precedent from KRAS G12D (134,000+ compounds) and antibody (≈5,000) campaigns [26,35]
7. Orthogonal physics-based validation	Docking + 100–300 ns MD + MM-GBSA on GNN-prioritized shortlist	Two-stage GNN-then-physics precedent [26,32]
8. Mechanistic stratification	Rank surviving hits by predicted partial-agonist/Ser273-blocking likelihood over full-agonist likelihood	Operationalizes SPPARγM design philosophy (Section 2) at screening scale

4. Core-Hopping and Scaffold-Hopping Strategies For PPARγ Modulator Design

Scaffold hopping the systematic replacement of a molecule's central core structure while retaining or improving its pharmacophoric and physicochemical profile is among the most productive medicinal chemistry strategies for escaping patent estate, resolving metabolic or toxicological liabilities tied to a specific chemotype, and fine-tuning selectivity. In an allosteric AKT inhibitor program, a ligand/structure-based core-hopping pipeline used the FDA-approved kinase-inhibitor core library as a source of replacement scaffolds for the triciribine template, yielding designed compounds with docking scores improved from approximately −8.6 kcal/mol (triciribine) to −11 to −13 kcal/mol, with MD confirming engagement of the same essential allosteric-site residues as the parent compound [44]. A structurally unrelated example in apoptosis biology replaced a complex hexahydrocyclopentaquinoline hit scaffold with a simplified phenylpyrrole core through iterative scaffold hopping, ultimately delivering a submicromolar BAX activator with a markedly more tractable synthetic route than the original hit [43].

Scaffold hopping has also proven decisive for antitubercular drug design, where ring expansion of the benzothiazinone (BTZ) core of the clinical candidate BTZ-043 into benzofuran- and naphthalene-fused thiazinones probed the electrochemical and covalent-binding requirements for DprE1 inhibition, clarifying which structural features are essential to retain versus which are modifiable [45]. In a liver-regeneration kinase program, changing the core heterocycle of the BRAF inhibitor vemurafenib from a pyrrolopyridine to a pyrazolopyridine while conserving the surrounding substituent vectors preserved off-target affinity for MKK4 while substantially improving selectivity against the mandatory anti-target panel (MKK7, JNK1) and known off-targets (BRAF, MAP4K5, ZAK) [47]. Similarly, natural-product scaffold hopping guided

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by pharmacophore modeling and iMODS-based normal-mode molecular dynamics identified koenimbine as a repositioned SARS-CoV-2/colorectal-cancer dual-activity candidate by systematically recombining phytoconstituent cores around a shared pharmacophore [46], and Biginelli-derived dihydropyrimidinone-pyrazole-benzofuran hybrid cores generated via scaffold hopping from the classical Eg5 inhibitor monastrol produced an analogue with superior growth-inhibitory activity in breast cancer cell lines [48].

These precedents converge on a transferable principle directly applicable to the PPAR-γ TZD core: the acidic head group (thiazolidine-2,4-dione, or its bioisosteric replacements such as gallic-acid-derived phenolic acids [11] or carboxylic/tetrazole isosteres) that anchors the Ser289/His323/His449/Tyr473 hydrogen-bond network is the pharmacophoric feature that must be conserved, while the aromatic linker and tail region connecting this head group to the Ω-loop and β-sheet coactivator-selectivity surface is the segment most amenable to core hopping. Because full-agonist TZDs achieve their H12-locking geometry through a very specific vector and rigidity of this linker-tail region, systematically varying scaffold rigidity, ring size, and vector geometry in this zone precisely the design lever demonstrated across the AKT, BAX, DprE1, and MKK4 case studies above offers a rational route to partial-agonist and biased-agonist PPAR-γ ligands that retain the essential head-group anchor while deliberately under-stabilizing H12.

Table 4. Cross-target scaffold/core-hopping case studies and transferable design principles for PPAR-γ

Target / Program	Original Core → New Core	Outcome	Transferable Principle for PPAR-γ	Ref.
Allosteric AKT1 inhibitors	Triciribine → FDA-approved kinase-inhibitor cores	Docking improved from −8.6 to −11/−13 kcal/mol	Mine approved-drug core libraries for AF-2-compatible replacement scaffolds	[44]
BAX activators (apoptosis)	Hexahydrocyclopentaquinoline → phenylpyrrole	Submicromolar activity with simplified synthesis	Simplify complex hit scaffolds while retaining key contact geometry	[43]
DprE1 / antitubercular (BTZ-043 series)	Benzothiazinone → benzofuran-/naphthalene-fused thiazinone	Clarified essential vs. modifiable covalent-binding features	Systematically map which TZD head-group features are truly essential	[45]
MKK4 / liver regeneration	Pyrrolopyridine (vemurafenib-derived) → pyrazolopyridine	Retained affinity, improved anti-target selectivity	Core swap can improve selectivity across the PPAR α/β/δ/γ subfamily	[47]

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SARS-CoV-2 / colorectal (natural product)	Multiple phytoconstituent cores → pharmacophore-recombined scaffold (koenimbine)	Dual-activity natural product candidate identified	Pharmacophore-guided recombination of natural PPAR-γ ligand fragments	[46]
Eg5 inhibitors (breast cancer)	Monastrol dihydropyrimidinone → DHPM-pyrazole-benzofuran hybrid	Improved growth-inhibitory activity vs. monastrol	Hybrid-core fusion as a route to novel TZD bioisosteres	[48]

5. An Integrated GNN + Core-Hopping Workflow for Rational PPAR-γ Modulator Design

The preceding sections establish that GNN-guided virtual screening and core-hopping are not competing strategies but sequential, complementary stages of a single design cycle. In the proposed integrated framework, GNN-based virtual screening (Section 5) is used first as a triage tool over ultra-large libraries to identify chemotypes with a favorable predicted mechanistic class (partial agonist or Ser273-blocking non-agonist rather than full agonist). The highest-confidence hits emerging from this stage typically a small number of chemically distinct clusters rather than close analogues, since scaffold-split-validated GNNs are specifically selected for generalization across chemotype boundaries then become the input scaffolds for the core-hopping stage (Section 6), in which the acidic head-group pharmacophore is held fixed while the linker-tail geometry is systematically varied using validated core libraries (approved-drug cores, natural-product fragments, or generative-model-proposed replacements; see Section 8) to modulate the degree of H12 engagement. Each core-hopped analogue re-enters the GNN scoring function for rapid re-ranking before the top tier is escalated to docking, extended MD (100–300 ns), and MM-GBSA/MM-PBSA binding free-energy decomposition for final mechanistic confirmation, mirroring the two-stage GNN-then-physics validation precedent established for other targets [26,32].

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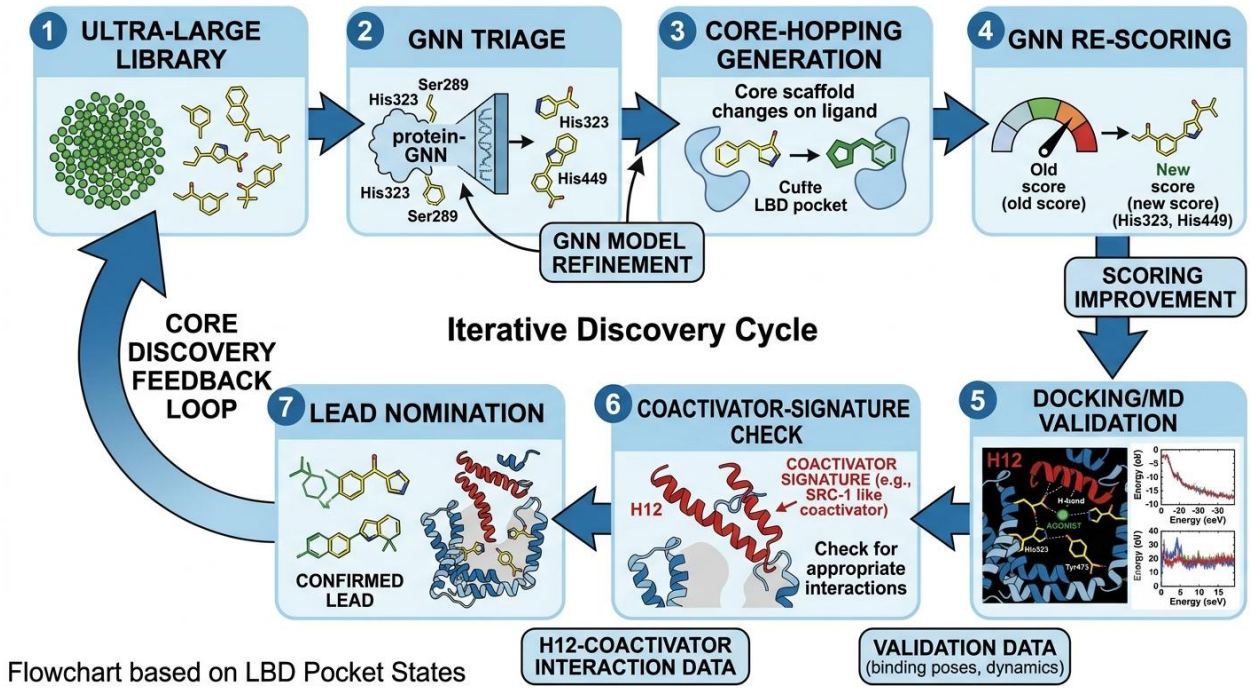

Figure2: Integrated GNN + Core-Hopping Design Cycle

Critically, this iterative loop should be explicitly informed by the biased-agonism structural mechanism described in Section 2: coactivator-recruitment profiling (whether computational, via MD-based interaction fingerprinting of the Ω-loop/β-sheet surface, or experimental, via peptide-recruitment assays) should be layered onto the affinity-driven GNN/docking cascade so that lead compounds are selected not merely for high predicted affinity but for the specific coactivator-recruitment signature associated with insulin-sensitizing, non-adipogenic pharmacology [8,9]. This coupling of mechanistic biophysics to computational screening distinguishes the proposed workflow from a conventional affinity-only virtual screening cascade and is, in the authors' assessment, the single most important design principle for translating GNN/core-hopping hits into genuinely differentiated PPAR-γ therapeutics.

Table 5. Integrated GNN + core-hopping design cycle mapped to decision criteria at each stage

Cycle Stage	Input	Computational Operation	Selection Criterion / Output
A. Primary GNN triage	Ultra-large virtual library (10^4–10^6 compounds)	Multi-task GNN classification (agonist class) + regression (affinity)	Chemically diverse clusters predicted as partial agonist / Ser273-blocker
B. Core-hopping generation	Prioritized clusters from stage A	Fix acidic head group; enumerate linker-tail replacements from approved-drug/natural-	Structurally novel analogues retaining Ser289/His323/His449/Tyr473 anchor

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		product/generative core libraries	
C. GNN re-scoring	Core-hopped analogue set	Re-apply trained GNN to re-rank by predicted class + affinity	Top-tier analogues advanced to physics-based validation
D. Physics-based validation	Top-tier analogues	Docking + 100–300 ns MD + MM-GBSA/MM-PBSA	Confirmed stable binding mode; quantified ΔG relative to reference agonist
E. Coactivator-signature check	MD trajectories of validated hits	Interaction fingerprinting of Ω-loop/β-sheet coactivator-selectivity surface	Preference for coactivator profile associated with insulin-sensitizing, non-adipogenic pharmacology [8,9]
F. Lead nomination	Compounds passing D and E	Integrated ranking across affinity, mechanistic class, and coactivator signature	Candidates nominated for synthesis and in vitro/in vivo evaluation

8. Design Strategies to Optimize Novel PPAR-γ Modulators

Beyond hit identification, several specific optimization strategies distinguish a well-designed PPAR-γ modulator program from a generic affinity-maximization campaign. First, partial agonism should be an explicit design target rather than an incidental outcome: ligands engineered to form a subset rather than the complete set of the H12-stabilizing hydrogen bonds engaged by full TZD agonists reproduce the favourable insulin-sensitizing transcriptional program while avoiding the adipogenic and fluid-retentive consequences of full agonism [7,10,11]. Second, Ser273-phosphorylation blockade represents a mechanistically distinct and, in several respects, more attractive optimization axis than classical transactivation, since ligands can in principle be optimized to occupy the LBD pocket in a manner that sterically or allosterically prevents CDK5 access to Ser273 without requiring transactivation-competent H12 stabilization at all [4]. Third, anti-inflammatory transrepression the ability of certain ligand-bound conformations to sequester NF-κB and AP-1 pathway components independent of classical DNA-binding transactivation offers a route to indications beyond metabolic disease, including chemoprevention in squamous carcinogenesis, and should be considered a parallel optimization objective where the therapeutic hypothesis warrants it [12].

Fourth, subfamily selectivity across PPAR-α, PPAR-β/δ, and PPAR-γ remains a first-order design consideration: dual PPAR-α/γ agonist programs illustrate that selectivity can be tuned through 3D-QSAR-guided substituent optimization [17] and virtual screening against isoform-specific pocket features [18,19,20], and the same computational infrastructure (isoform-specific GNN classification heads, isoform-specific docking grids) can be repurposed to explicitly disfavor off-target PPAR-α/δ engagement where isoform selectivity is the therapeutic goal. Fifth, generative and reinforcement-learning-based de novo

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design methods including REINVENT-style policy-gradient generation constrained by multiparameter scoring functions that combine predicted affinity, blood-brain-barrier or peripheral-restriction requirements, and synthetic accessibility [38,39,40] provide a natural mechanism for populating the core-hopping library described in Section 6 with chemically valid, synthetically tractable candidate cores beyond those available in curated approved-drug or natural-product databases, and free-energy-perturbation-refined generative pipelines offer a route to quantitatively rank closely related analogues once a promising core has been identified [41]. Sixth, and finally, downstream pharmacokinetic and drug-likeness filtering using graph-based PBPK/CGCNN pharmacokinetic prediction [34] and ensemble drug-likeness scoring frameworks [42] should be integrated early in the cascade rather than applied only after lead nomination, since oral bioavailability and hepatic/renal clearance profiles have historically been decisive differentiators among clinically successful versus abandoned PPAR-γ chemical series.

Table 6. Design strategies for optimizing novel PPAR-γ modulators

Optimization Axis	Mechanistic Rationale	Computational Enabling Tool	Ref.
Partial agonism / SPPARγM design	Retains insulin sensitization; avoids full H12 stabilization and adipogenesis	GNN mechanistic-class classification; docking-based partial H-bond-network scoring	[7,10,11]
Ser273-phosphorylation blockade	Decouples insulin sensitization from classical transactivation entirely	MD-based accessibility mapping of CDK5 phosphorylation site	[4]
Anti-inflammatory transrepression bias	NF-κB/AP-1 sequestration independent of DNA binding; chemopreventive potential	Coactivator/corepressor interaction fingerprinting	[6,12]
PPAR α/β/δ subfamily selectivity	Minimizes off-target isoform pharmacology; tunable via substituent SAR	Isoform-specific GNN heads; comparative docking grids	[17,18,19,20]
Generative / RL-guided core proposal	Populates core-hopping library beyond curated databases; multiparameter-optimized	REINVENT-style policy-gradient / VAE generative models	[38,39,40,41]
Early ADMET / drug-likeness triage	Historically decisive for clinical translation of PPAR-γ chemical series	Graph-based PBPK/CGCNN; ensemble drug-likeness scoring	[34,42]

9. Challenges and Limitations

Several limitations temper enthusiasm for a purely computational path to next-generation PPAR-γ modulators. Target-specific training data remain a genuine constraint: unlike oncology kinase targets, for which tens of thousands of annotated bioactivity records support robust GNN training, the PPAR-γ literature while extensive in absolute terms contains comparatively few entries explicitly annotated by mechanistic class (full agonist versus partial agonist versus SPPARγM versus inverse agonist versus

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Ser273-blocker), and model performance on this more granular, clinically decisive classification task will necessarily lag behind simple binary active/inactive prediction until better-curated training sets are assembled. Docking and MM-GBSA scoring functions, while broadly reliable for relative ranking within a congeneric series, remain imprecise for absolute free-energy prediction across structurally diverse core-hopped scaffolds, meaning that GNN/docking-prioritized hits must still be treated as hypotheses requiring experimental confirmation rather than definitive predictions. GNN models are further subject to well-documented interpretability limitations the 'black-box' critique which is particularly consequential in a target area where the mechanistic distinction between beneficial partial agonism and harmful full agonism can hinge on subtle differences in a small number of hydrogen-bond geometries that a purely affinity-trained model may not explicitly capture unless mechanistic-class labels are deliberately incorporated into training, as recommended in Section 5. Finally, generalizability across genuinely novel core-hopped scaffolds is intrinsically limited by the applicability domain of the training data; scaffold-split validation mitigates but does not eliminate this risk, and experimental triage of even computationally prioritized hits therefore remains indispensable.

10. Future Perspectives

Several near-term methodological developments are likely to strengthen the integrated GNN/core-hopping framework proposed here. Active-learning loops that iteratively retrain the GNN on newly generated experimental data from each design cycle should progressively sharpen mechanistic-class discrimination with far fewer total compounds synthesized than a static-model campaign would require. Incorporation of MD-refined, rather than purely docked, poses into GNN training data feeding the model three-dimensional interaction fingerprints time-averaged over simulation trajectories rather than single static docking poses — should improve the model's ability to distinguish the subtle H12-engagement differences that separate full from partial agonists. Explainable-AI techniques applied to trained GNNs, which can highlight which substructural motifs or atom-level contributions drive a given mechanistic-class prediction, would directly address the interpretability limitation noted above and could, in principle, surface previously unappreciated pharmacophoric features relevant to biased agonism. Finally, tighter integration of generative de novo design with the core-hopping paradigm described in Section 6 using reinforcement-learning or diffusion-based generative models constrained simultaneously by predicted affinity, mechanistic-class probability, synthetic accessibility, and PBPK-predicted pharmacokinetics represents a natural extension of the multiparameter-optimization generative frameworks already demonstrated for other CNS- and oncology-targeted programs [38,40,41] to the specific, mechanistically nuanced requirements of PPAR-γ modulator discovery.

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11. Conclusion

PPAR-γ exemplifies a target class in which maximal receptor engagement is not synonymous with optimal therapeutic outcome, and where decades of structural biology have converged on a nuanced pharmacological objective selective, partial, or biased modulation that classical high-throughput screening and simple affinity-maximization campaigns are poorly suited to deliver. Graph neural networks, by learning directly from the topological and, where available, three-dimensional structural language of ligand-receptor interaction, offer a route to screening chemical space at a scale and mechanistic granularity previously unattainable, while core-hopping provides the medicinal chemistry mechanism through which the resulting insights are translated into structurally novel, synthetically tractable candidate molecules. The integrated workflow proposed in this review GNN-guided triage, core-hopping-based scaffold diversification, GNN re-scoring, physics-based validation, and explicit coactivator-signature confirmation — is offered as a practical framework for medicinal and computational chemists pursuing the next generation of PPAR-γ therapeutics, and its underlying logic (mechanistic-class-aware screening coupled to scaffold-preserving core diversification) is, in the authors' view, readily generalizable to other nuclear receptor and allosterically nuanced drug targets beyond PPAR-γ itself. Indeed, the broader precedent for structure-based virtual screening coupled with molecular dynamics validation extends well beyond nuclear receptor pharmacology: analogous pipelines combining natural-compound virtual screening with MD simulation successfully prioritized candidate inhibitors of the SARS-CoV-2 spike receptor from large natural-product libraries during the COVID-19 pandemic [51], while structurally similar docking-and-dynamics workflows have guided the rational design of epoxide-functionalized 1,2,4-trioxane antimalarial agents [52]. These examples, spanning viral entry inhibition and antiparasitic chemotherapy, reinforce that the docking/MD/MM-GBSA validation layer at the core of the present GNN-plus-core-hopping framework is a mature, broadly transferable methodology rather than a PPAR-γ-specific expedient. As GNN-based triage and generative core-hopping mature alongside this established physics-based validation infrastructure, the same integrated logic proposed here for PPAR-γ modulator discovery should extend readily to other structurally characterized, pharmacologically nuanced drug targets across therapeutic areas.

References

1. Gupta, O., Pradhan, T., Chawla, G., 2025. Structural and functional insights into PPAR-γ: review of its potential and drug design innovations for the development of antidiabetic agents. Eur. J. Med. Chem. 302(Pt 1), 118264. https://doi.org/10.1016/j.ejmech.2025.118264
2. Singh, A., Chaudhary, R., 2025. Potentials of peroxisome proliferator-activated receptor (PPAR) α, β/δ, and γ: an in-depth and comprehensive review of their molecular mechanisms, cellular signalling, immune responses and therapeutic implications in multiple diseases. Int. Immunopharmacol. 155, 114616. https://doi.org/10.1016/j.intimp.2025.114616

https://doi.org/10.71058/jodac.v10i0712

3. Colca, J.R., Tanis, S.P., Kletzien, R.F., Finck, B.N., 2023. Insulin sensitizers in 2023: lessons learned and new avenues for investigation. Expert Opin. Investig. Drugs 32(9), 803-811. https://doi.org/10.1080/13543784.2023.2263369

4. Frkic, R.L., Richter, K., Bruning, J.B., 2021. The therapeutic potential of inhibiting PPARγ phosphorylation to treat type 2 diabetes. J. Biol. Chem. 297(3), 101030. https://doi.org/10.1016/j.jbc.2021.101030

5. Lee, M.A., Tan, L., Yang, H., Im, Y.G., Im, Y.J., 2017. Structures of PPARγ complexed with lobeglitazone and pioglitazone reveal key determinants for the recognition of antidiabetic drugs. Sci. Rep. 7(1), 16837. https://doi.org/10.1038/s41598-017-17082-x

6. Irwin, S., Karr, C., Furman, C., Tsai, J., Gee, P., Banka, D., Wibowo, A.S., Dementiev, A.A., O'Shea, M., Yang, J., Lowe, J., Mitchell, L., Ruppel, S., Fekkes, P., Zhu, P., Korpal, M., Larsen, N.A., 2022. Biochemical and structural basis for the pharmacological inhibition of nuclear hormone receptor PPARγ by inverse agonists. J. Biol. Chem. 298(11), 102539. https://doi.org/10.1016/j.jbc.2022.102539

7. Yi, W., Shi, J., Zhao, G., Zhou, X.E., Suino-Powell, K., Melcher, K., Xu, H.E., 2017. Identification of a novel selective PPARγ ligand with a unique binding mode and improved therapeutic profile in vitro. Sci. Rep. 7, 41487. https://doi.org/10.1038/srep41487

8. Nemetchek, M.D., Chrisman, I.M., Rayl, M.L., Voss, A.H., Hughes, T.S., 2022. A structural mechanism of nuclear receptor biased agonism. Proc. Natl. Acad. Sci. U.S.A. 119(50), e2215333119. https://doi.org/10.1073/pnas.2215333119

9. Rayl, M.L., Nemetchek, M.D., Voss, A.H., Hughes, T.S., 2024. Agonists of the nuclear receptor PPARγ can produce biased signaling. Mol. Pharmacol. 106(6), 309-318. https://doi.org/10.1124/molpharm.124.000992

10. Guasch, L., Sala, E., Castell-Auví, A., Cedó, L., Liedl, K.R., Wolber, G., Muehlbacher, M., Mulero, M., Pinent, M., Ardévol, A., Valls, C., Pujadas, G., Garcia-Vallvé, S., 2012. Identification of PPARgamma partial agonists of natural origin (I): development of a virtual screening procedure and in vitro validation. PLoS ONE 7(11), e50816. https://doi.org/10.1371/journal.pone.0050816

11. Aryan, Babu, B., Divakar, S., Gowramma, B., Jupudi, S., Chand, J., Malakar Kumar, V., 2023. Rational design of thiazolidine-4-one-gallic acid hybrid derivatives as selective partial PPARγ modulators: an in-silico approach for type 2 diabetes treatment. J. Biomol. Struct. Dyn. 43(2), 694-708. https://doi.org/10.1080/07391102.2023.2283161

12. Ren, L., Konger, R.L., 2019. Evidence that peroxisome proliferator-activated receptor γ suppresses squamous carcinogenesis through anti-inflammatory signaling and regulation of the immune response. Mol. Carcinog. 58(9), 1589-1601. https://doi.org/10.1002/mc.23041

13. Miehle, K., Porrmann, J., Mitter, D., Stumvoll, M., Glaser, C., Fasshauer, M., Hoffmann, K., 2015. Novel peroxisome proliferator-activated receptor gamma mutation in a family with familial partial lipodystrophy type 3. Clin. Endocrinol. 84(1), 141-148. https://doi.org/10.1111/cen.12837

14. Lori, C., Pasquo, A., Montanari, R., Capelli, D., Consalvi, V., Chiaraluce, R., Cervoni, L., Loiodice, F., Laghezza, A., Aschi, M., Giorgi, A., Pochetti, G., 2014. Structural basis of the transactivation deficiency of the human PPARγ F360L mutant associated with familial partial lipodystrophy. Acta Crystallogr. D Biol. Crystallogr. 70(Pt 7), 1965-1976.https://doi.org/10.1107/S1399004714009638

https://doi.org/10.71058/jodac.v10i0712

15. Lu, J., Dawson, M.I., Hu, Q.Y., Xia, Z., Dambacher, J.D., Ye, M., Zhang, X.K., Li, E., 2009. The effect of antagonists on the conformational exchange of the retinoid X receptor alpha ligand-binding domain. Magn. Reson. Chem. 47(12), 1071-1080. https://doi.org/10.1002/mrc.2515

16. Lokhande, K.B., Ballav, S., Yadav, R.S., Swamy, K.V., Basu, S., 2020. Probing intermolecular interactions and binding stability of kaempferol, quercetin and resveratrol derivatives with PPAR-γ: docking, molecular dynamics and MM/GBSA approach to reveal potent PPAR-γ agonist against cancer. J. Biomol. Struct. Dyn. 40(3), 971-981. https://doi.org/10.1080/07391102.2020.1820380

17. Liu, Y.Y., Feng, X.Y., Jia, W.Q., Jing, Z., Xu, W.R., Cheng, X.C., 2019. Virtual identification of novel PPARα/γ dual agonists by 3D-QSAR, molecule docking and molecular dynamics studies. J. Biomol. Struct. Dyn. 38(9), 2672-2685. https://doi.org/10.1080/07391102.2019.1656110

18. Niu, H., Wang, W., Li, J., Lei, Y., Zhao, Y., Yang, W., Zhao, C., Lin, B., Song, S., Wang, S., 2017. A novel structural class of coumarin-chalcone fibrates as PPARα/γ agonists with potent antioxidant activities: design, synthesis, biological evaluation and molecular docking studies. Eur. J. Med. Chem. 138, 212-220. https://doi.org/10.1016/j.ejmech.2017.06.033

19. Gao, Q., Hanh, J., Váradi, L., Cairns, R., Sjöström, H., Liao, V.W.Y., Wood, P., Balaban, S., Ong, J.A., Lin, H.Y.J., Lai, F., Hoy, A.J., Grewal, T., Groundwater, P.W., Hibbs, D.E., 2015. Identification of dual PPARα/γ agonists and their effects on lipid metabolism. Bioorg. Med. Chem. 23(24), 7676-7684. https://doi.org/10.1016/j.bmc.2015.11.013

20. Kato, T., Ohara, T., Suzuki, N., Muto, S., Tokuyama, R., Mizutani, M., Fukasawa, H., Matsumura, K.I., Itai, A., 2022. Discovery and structure-based design of a new series of potent and selective PPARδ agonists utilizing a virtual screening method. Bioorg. Med. Chem. Lett. 59, 128567. https://doi.org/10.1016/j.bmcl.2022.128567

21. Gharge, S., Alegaon, S.G., Ranade, S.D., Kavalapure, R.S., Prashantha Kumar, B.R., Mhaske, P.C., 2024. Expression of PPAR-γ TF by newly synthesized thiazolidine-2,4-diones to manage glycemic control: insights from in silico, in vitro and experimental pharmacology in wistar rats. Bioorg. Chem. 153, 107966. https://doi.org/10.1016/j.bioorg.2024.107966

22. Gupta, S., Baweja, G.S., Singh, S., Irani, M., Singh, R., Asati, V., 2023. Integrated fragment-based drug design and virtual screening techniques for exploring the antidiabetic potential of thiazolidine-2,4-diones: design, synthesis and in vivo studies. Eur. J. Med. Chem. 261, 115826. https://doi.org/10.1016/j.ejmech.2023.115826

23. Omoboyowa, D.A., Singh, G., Fatoki, J.O., Oyeneyin, O.E., 2022. Computational investigation of phytochemicals from Abrus precatorius seeds as modulators of peroxisome proliferator-activated receptor gamma (PPARγ). J. Biomol. Struct. Dyn. 41(12), 5568-5582. https://doi.org/10.1080/07391102.2022.2091657

24. Senthil, R., Sakthivel, M., Usha, S., 2020. Structure-based drug design of peroxisome proliferator-activated receptor gamma inhibitors: ferulic acid and derivatives. J. Biomol. Struct. Dyn. 39(4), 1295-1311. https://doi.org/10.1080/07391102.2020.1740790

25. Huang, L., Fang, Z., Han, R., Tong, X., 2026. Identification of phillyrin as a PPAR-γ ligand through network pharmacology and molecular modeling. NPJ Syst. Biol. Appl. https://doi.org/10.1038/s41540-026-00780-6

https://doi.org/10.71058/jodac.v10i0712

26. Zhou, C., Zhu, Y., Yang, C., Gao, Y., Lu, J., Ming, D., 2026. A molecular-protein fusion framework for rapid virtual screening: accelerating lead discovery for 'undruggable' oncogenic targets. Pharmaceuticals 19(5), 753. https://doi.org/10.3390/ph19050753

27. Murala, D.K., Panda, S.K., 2026. Multimodal machine learning and deep graph neural networks for the prediction of molecular inhibitory activity and disease associations. J. Comput. Aided Mol. Des. 40(1). https://doi.org/10.1007/s10822-026-00858-7

28. Le, V.V., Nhu, M.T.A., Thong, P.T.V., 2026. GraphTransDTI: a novel hybrid framework combining graph transformer and CNN-BiLSTM for enhanced drug-protein interaction prediction. PLoS ONE 21(7), e0351314. https://doi.org/10.1371/journal.pone.0351314

29. Chen, Y., Huang, J., Liu, C., Zhang, S., Li, X., Zhang, Z., Chen, T.G., Wang, L., 2026. DualPG-DTA: a large language model-powered graph neural network framework for enhanced drug-target affinity prediction and discovery of novel CDK9 inhibitors exhibiting in vivo anti-leukemia activity. Adv. Sci. 13(12), e13099. https://doi.org/10.1002/advs.202513099

30. Jha, A., Suyash, S., Govindh, M., Maitra, P., Punia, P., Mishra, A., 2026. DecoyFinderNetAna: application of graph convolution neural networks for accurate classification of true small molecule binders from their decoys. Curr. Comput. Aided Drug Des. https://doi.org/10.2174/0115734099429333260113070143

31. Kala, P.P., Sakthidhasan, P., Gandhi, S., Vethamonickam, S.R., 2025. Convolutional neural network-assisted screening of natural product inhibitors against Naja naja venom: insights from molecular docking, molecular dynamics simulations and ADMET profiling. In Silico Pharmacol. 14(1), 13. https://doi.org/10.1007/s40203-025-00527-x

32. Cho, S.C., Wang, Y.W., Chu, C.A., Huang, M.C., Pangging, M., Lee, C.T., 2026. Discovery of WRN helicase inhibitors by 3D-CNN docking and ML consensus from traditional Chinese medicine monomers. J. Mol. Graph. Model. 146, 109376. https://doi.org/10.1016/j.jmgm.2026.109376

33. Monsia, R., Gundry, S.C., Mohr, M.L., Smith, M.A., Bhattacharyya, S., Hati, S., 2025. Graph convolutional neural network-enabled frontier molecular orbital prediction: a case study with neurotransmitters and antidepressants. J. Chem. Inf. Model. 65(14), 7447-7462. https://doi.org/10.1021/acs.jcim.5c00724

34. Hasegawa, K., Seki, Y., 2026. Computational hybrid approach of PBPK simulation and CGCNN models for human intravenous pharmacokinetics. Bioorg. Med. Chem. 140, 118731. https://doi.org/10.1016/j.bmc.2026.118731

35. Li, J., Ige, M.A., Zhang, C., Liao, L., Rasul, F., Ren, X., Wan, X., Chen, Y., Zhang, H., 2026. A bio-inspired computational pipeline for antibody screening and repurposing. Brief. Bioinform. 27(2). https://doi.org/10.1093/bib/bbag183

36. Sharma, Y., Das, A., 2026. Synergistic geroprotectors mapping through systems machine learning and graph neural networks. OMICS. https://doi.org/10.1177/15578100261464019

37. Spoendlin, F.C., Fernández-Quintero, M.L., Raghavan, S.S.R., Turner, H.L., Gharpure, A., Loeffler, J.R., Wong, W.K., Bujotzek, A., Georges, G., Ward, A.B., Deane, C.M., 2025. Predicting the conformational flexibility of antibody and T cell receptor complementarity-determining regions. Nat. Mach. Intell. 7(10), 1755-1767. https://doi.org/10.1038/s42256-025-01131-6

https://doi.org/10.71058/jodac.v10i0712

38. Murala, D.K., 2026. Geometric deep reinforcement learning with hierarchical variational autoencoders for de novo drug design and activity optimization. J. Comput. Aided Mol. Des. 40(1). https://doi.org/10.1007/s10822-026-00812-7

39. Sampa, M.B., Aziz, N.H.A., 2026. Application of reinforcement learning techniques in de novo drug design: a systematic literature review. Health Sci. Rep. 9(3), e72132. https://doi.org/10.1002/hsr2.72132

40. Persico, M., Micoli, A., Salmaso, V., Cianciulli, A., Moro, S., Spalluto, G., Buccioni, M., Marucci, G., Volpini, R., Pozzan, A., Micheli, F., Federico, S., 2026. Applying deep-learning-driven design to hit identification: a case study on A2A adenosine receptor antagonists. J. Med. Chem. 69(13), 15403-15422. https://doi.org/10.1021/acs.jmedchem.6c00231

41. Islam, M.A., Ali, M.A., Chikhale, R., Islam, M.L., Wabaidur, S.M., 2026. Free energy perturbation-assisted identification of checkpoint kinase 1 targeted small-molecule inhibitors for cancer therapy using AI- and physics-driven molecular design. Comput. Biol. Chem. 124(Pt 2), 109203. https://doi.org/10.1016/j.compbiolchem.2026.109203

42. Alsarra, I.A., Chikhale, R., Al-Mohizea, A.M., Islam, M.A., 2026. Identification of GPI-anchored wall transfer protein 1 modulators for fungal infections through generative AI and physics-based approaches. Int. J. Mol. Sci. 27(11). https://doi.org/10.3390/ijms27114767

43. Petrosyan, N., Matevosyan, H., Tirosyan, I., Gabrielyan, Y., Gevorgyan, S., Harutyunyan, V., Matevosyan, M., Zakaryan, H., 2026. Machine learning-based soft voting ensemble model for the prediction of oral drug-likeness of chemical structures. J. Chem. Inf. Model. https://doi.org/10.1021/acs.jcim.5c02953

44. Jang, Y.E., Kwon, M., Kwon, C.W., Kim, S.G., Hwang, J.S., George, N.P., Paik, S.R., Misra, S., Basith, S., Sheen, S.S., Lee, G., 2026. Integrative peptide drug development: chemical engineering, AI-driven design, and cell-penetrating peptides. Pharmaceutics 18(5), 537. https://doi.org/10.3390/pharmaceutics18050537

45. Poustforoosh, A., 2024. Scaffold hopping method for design and development of potential allosteric AKT inhibitors. Mol. Biotechnol. 67(10), 3960-3974. https://doi.org/10.1007/s12033-024-01307-2

46. Cai, W., Li, Z., Zhao, M., Gu, Y., Qiu, C., Zhou, M., Deng, W., Zhou, L., Li, Y., Wang, R., 2026. Design, synthesis, and evaluation of phenylpyrrole derivatives as small-molecule activators of BAX. J. Med. Chem. 69(7), 7541-7571. https://doi.org/10.1021/acs.jmedchem.5c02670

47. Keiff, F., Jacques Dit Lapierre, T.J.W., Bernal, F.A., Kloss, F., 2023. Design and synthesis of benzofuran- and naphthalene-fused thiazinones as antimycobacterial agents. Arch. Pharm. (Weinheim) 356(11), e2300356. https://doi.org/10.1002/ardp.202300356

48. Pakrashy, S., Mandal, P.K., Dey, S.K., Choudhury, S.M., Alasmary, F.A., Almalki, A.S., Islam, M.A., Dolai, M., 2022. Design of a structurally novel multipotent drug candidate by the scaffold architecture technique for ACE-II, NSP15, and M-protein inhibition. ACS Omega 7(37), 33408-33422. https://doi.org/10.1021/acsomega.2c04051

49. Pfaffenrot, B., Klövekorn, P., Juchum, M., Selig, R., Albrecht, W., Zender, L., Laufer, S.A., 2021. Design and synthesis of 1H-pyrazolo[3,4-b]pyridines targeting mitogen-activated protein kinase

https://doi.org/10.71058/jodac.v10i0712

kinase 4 (MKK4) - a promising target for liver regeneration. Eur. J. Med. Chem. 218, 113371. https://doi.org/10.1016/j.ejmech.2021.113371

50. Nikam, D., Jain, A., Vetale, S., Bhange, A., Jadhav, S., 2025. Targeting breast cancer: novel dihydropyrimidinones as potent Eg5 inhibitors. Med. Chem. 21(8), 866-879. https://doi.org/10.2174/0115734064336338241112043509

51. Sarkar, A., Sen, D., Sharma, A., et al., 2021. Structure-based virtual screening and molecular dynamics simulation to identify potential SARS-CoV-2 spike receptor inhibitors from natural compound database. Pharm. Chem. J. 55, 441-453. https://doi.org/10.1007/s11094-021-02441-w

52. Kumari, A., Karnatak, M., Sen, D., et al., 2022. Synthesis, molecular docking and dynamics study of novel epoxide derivatives of 1,2,4-trioxanes as antimalarial agents. Struct. Chem. 33, 907-919. https://doi.org/10.1007/s11224-022-01885-4