Available online on 15.11.2025 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2025 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Research Article

Artificial Intelligence (AI) Assisted Discovery of Novel FXR Agonists for NASH Treatment

Guy Müller Banquet Okra ^{1,2} , Mona Hermann Charly Yapi ^{1,2} , Koffi N'Guessan Placide Gabin Allangba ^{2,3,4} , Koffi Charles Kouman ² , Yves Kily Hervé Fagnidi ^{*2,5} , Kré N. Raymond ²

¹ Laboratory of Environmental Sciences and Technologies, Jean Lorougnon Guédé University, Ivory Coast.

² Applied Fundamental Physics Laboratory (LPFA), Nangui Abrogoua University, Ivory Coast.

³ Laboratory of Biophysics and Nuclear Medicine (LBNM), Félix Houphouët-Boigny University, Ivory Coast.

⁴ Department of Medical Physics, University of Trieste and International Centre for Theoretical Physics (ICTP), Trieste, Italy

⁵ Training and Research Unit in Science and Technology, Alassane Ouattara University of Bouaké, Ivory Coast

Article Info:

Abstract



Article History:

Received 18 Aug 2025

Reviewed 11 Oct 2025

Accepted 30 Oct 2025

Published 15 Nov 2025

Cite this article as:

Okra GMB, Yapi MHC, Allangba KNPG, Kouman KC, Fagnidi YKH, Raymond KN, Artificial Intelligence (AI) Assisted Discovery of Novel FXR Agonists for NASH Treatment, Journal of Drug Delivery and Therapeutics. 2025; 15(11):9-16 DOI: <http://dx.doi.org/10.22270/jddt.v15i11.7449>

*For Correspondence:

Yves Kily Hervé Fagnidi, Applied Fundamental Physics Laboratory (LPFA), Nangui Abrogoua University, Ivory Coast.

Background: Non-alcoholic steatohepatitis (NASH) is a chronic metabolic disease characterized by lipid accumulation, inflammation, and progressive liver fibrosis. The lack of approved treatments highlights the need to identify new agonists of the farnesoid X receptor (FXR), a key regulator of lipid metabolism and bile acids.

Methods: An integrated AI-assisted drug discovery pipeline was developed, combining a QSAR model based on graph neural networks (GraphConvModel), high-throughput virtual screening, in silico ADMET evaluation, and molecular docking. The model was trained on 3,450 ligands from ChEMBL and PubChem, then applied to screen approximately one million additional molecules from PubChem.

Results: The model achieved high performance ($R^2 = 0.89$), reproducing the experimental activity hierarchy. Successive filters (Lipinski, bioavailability, DILI, hERG) led to nine candidate agonists, with molecules M9 (CID: 7190831) and M1 (CID: 8888557) showing the best docking scores (-49.37 and -49.11 kcal/mol). Their stable interactions with residues PHE363, ILE359, TYR358, and TRP451 confirm their agonist potential.

Conclusion: The AI-ADMET-Docking pipeline is a rapid and reliable predictive tool for discovering FXR agonists. These results validate the value of AI in researching innovative treatments for NASH and pave the way for experimental validation of molecule M9 (CID: 7190831).

Keywords: FXR, NASH/MASH, molecular modeling, Artificial Intelligence, Graph Neural Networks (GNN)

INTRODUCTION

Non-Alcoholic Steatohepatitis (NASH), today known as MASH (Metabolic dysfunction-Associated Steatohepatitis) is currently one of the leading causes of morbidity and mortality related to metabolic diseases¹. It is predicted to become the leading indication for liver transplantation by 2030, posing a significant burden on global health². Representing the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), it is characterized by excessive triglyceride accumulation in hepatocytes, coupled with chronic inflammation and hepatic fibrosis. Recent estimates indicate that MASH affects over 25% of the global population, with its prevalence continuing to rise alongside obesity, type 2 diabetes, and metabolic syndrome³. Despite recent advances, including the FDA approvals of resmetirom (Rezdiffra) in March 2024 and

semaglutide (Wegovy) in August 2025 as the first and second treatments for NASH with moderate-to-advanced fibrosis, the therapeutic landscape remains limited, with many patients experiencing incomplete responses or side effects^{4,5}. This underscores the urgent need for innovative targeted therapies⁶.

At the heart of NASH pathophysiology lies the farnesoid X receptor (FXR), a nuclear receptor primarily expressed in the liver, intestine, and kidneys. FXR serves as a key regulator of bile acid homeostasis, lipid metabolism, and hepatic gluconeogenesis⁷. Its activation reduces hepatic fat accumulation, modulates inflammation, and promotes antifibrotic effects, positioning FXR as a strategic pharmacological target for NASH⁸.

Several FXR agonists have been developed and evaluated in clinical trials, including obeticholic acid (OCA), tropifexor, and cilofexor^{9–11}. While these compounds have demonstrated benefits on histological and metabolic markers, their clinical progress has been hampered by severe adverse effects, such as pruritus, elevated LDL cholesterol, and hepatic toxicity in patients with advanced cirrhosis¹². As of 2025, OCA remains approved only for primary biliary cholangitis (PBC), with its NASH application still under review following prior FDA rejections¹³. These limitations highlight the need for new FXR agonists that maintain comparable efficacy while offering an improved pharmacokinetic and safety profile¹⁴.

In this context, modern computational approaches grounded in artificial intelligence (AI) provide a unique opportunity to accelerate and rationalize drug candidate discovery^{15,16}. Deep learning, particularly graph neural networks (GNNs), enables direct modeling of structure-activity relationships from molecular graphs without manual descriptor engineering. Combined with high-throughput virtual screening and in silico ADMET modeling, this method filters millions of molecules by simultaneously predicting affinity, bioavailability, and safety¹⁷.

The present study proposes an integrative AI-assisted strategy to identify novel FXR agonists with enhanced therapeutic potential against MASH. Our approach integrates (i) an advanced QSAR model based on graph neural networks (GraphConvModel), (ii) large-scale virtual screening of over one million PubChem compounds, and (iii) comparative assessment of ADMET properties and docking interactions with crystallized FXR (PDB ID: 1OSV)^{18–20}.

MATERIALS AND METHODS

1. Computational Environment

All calculations were performed on the Google Colab platform in a Python 3.12 environment²¹. The main libraries used included: RDKit for generating, manipulating, and converting molecular structures; DeepChem (v2.6.0) for data preparation and implementation of the deep learning model; PyTorch (v2.8.0+cu126) and torch-geometric (2.7.0) for graph-based neural modeling. Executions were performed on standard CPU without GPU acceleration. This modest configuration proved sufficient for training and inference of the GraphConv model.

2. Data and Dataset Preparation

Ligands of the farnesoid X receptor (FXR, UniProt: Q96RI1, ChEMBL ID: ChEMBL2047) with experimental affinity values (EC_{50}) were extracted from the ChEMBL database^{22,23}. The initial set of 321 ligands was enriched by a structural similarity search in PubChem¹⁹, resulting in a total corpus of 3,600 compounds. After removing duplicates and normalizing structures (generation of canonical SMILES and charge neutralization), 3,435 unique molecules were retained. Affinity values were converted to $pEC_{50} = -\log_{10}(EC_{50})$ to normalize the distribution and improve learning stability.

The data were randomly split according to a stratified distribution: Training: 80%, Validation: 10%, Test: 10%. The sets were standardized and stored in CSV format for experiment reproducibility.

3. Graph Neural Network-Based QSAR Modeling (GraphConv)

The biological activity modeling was performed using a GraphConvModel (Graph Convolutional Neural Network, GCN). Each molecule was represented as a graph, with atoms as nodes and chemical bonds as edges, allowing the model to capture the complete molecular topology^{24,25}. The model architecture included: three successive convolutional layers (128, 64, and 32 neurons), ReLU activation functions, dropout regularization = 0.2, global average pooling to aggregate atomic representations, and a fully connected layer for final pEC_{50} prediction. Optimization was performed via the Adam algorithm (learning rate = 0.0005, L2 regularization = 1×10^{-4}). The loss function used was MSE (Mean Squared Error), with early stopping (patience = 10) on validation MSE. Each training ran for a maximum of 150 epochs. Performance was evaluated on the test set using: R^2 (coefficient of determination), MAE (Mean Absolute Error), RMSE (Root Mean Squared Error). A 5-fold cross-validation ($k = 5$) was performed to confirm model robustness and limit overfitting.

4. Validation of Experimental Consistency

The QSAR model performance was validated on four reference FXR agonists (GW4064, OCA, tropifexor, cilofexor) to compare experimental and predicted pEC_{50} values. This step confirmed the model's ability to reproduce the activity hierarchy among known agonists, while highlighting the need for fine calibration of absolute predictions.

5. High-Throughput Virtual Screening

The trained model was applied to a library of approximately 1,000,000 compounds from PubChem. SMILES were converted to molecular graphs with RDKit, then subjected to pEC_{50} prediction. Preselection criteria were: $pEC_{50} \geq 7.0$ (high activity), compliance with Lipinski's rule [16], QED > 0.6 (favorable drug-likeness). A complementary filter based on structural compatibility with the FXR pocket (hydrophobic cycles like cyclohexane) reduced the library to 694 final candidates²⁶.

6. ADMET Properties Evaluation

The pharmacokinetic and safety properties of the 694 candidates were evaluated using RDKit and the ADMETLab 3.0 platform. Filter criteria were: PPB > 90% (high plasma binding), BBB < 0.5 (low brain penetration), DILI < 0.5 (low predicted hepatotoxicity), Caco-2 > -5.5 (good intestinal permeability), no violations of Pfizer or GSK rules. Nine molecules—M1 (CID: 8888557), M2 (CID: 22216658), M3 (CID: 8422059), M4 (CID: 7190756), M5 (CID: 18163764), M6 (CID: 8422070), M7 (CID: 10494847), M8 (CID: 84221227), M9 (CID: 7190831)—met these criteria and were retained for in-depth analysis.

7. Molecular Docking

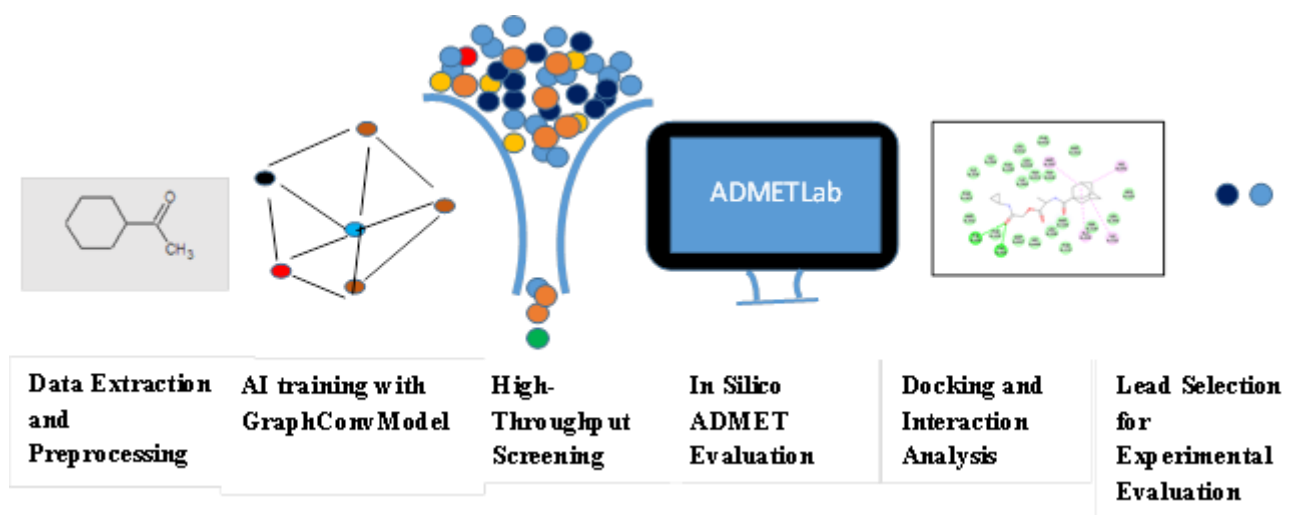


Figure 1: integrated AI-assisted discovery pipeline

The 3D structures of the retained ligands were downloaded from PubChem. The crystallographic structure of the FXR ligand-binding domain (LBD) (PDB ID: 1OSV, complexed with OCA) was prepared with Discovery Studio²⁷: removal of water molecules, addition of polar hydrogens, CHARMM force field optimization, definition of a grid centered on the co-crystallized ligand. Each ligand was subjected to ten docking poses, ranked by interaction energy. Hydrogen, hydrophobic, and π -alkyl interactions were analyzed using the 2D Diagram module. Figures were interpreted to identify key residues involved in stabilizing the

ligand-FXR complex. The full pipeline is presented in Figure 1.

RESULTS

1. Prediction Model Performance

The GraphConvModel, based on graph neural networks, demonstrated strong predictive capability for pEC_{50} values of FXR receptor ligands.

On the test set, cross-validation ($k = 5$) yielded: $R^2 = 0.89 \pm 0.03$, $MSE = 0.33 \pm 0.08$, $MAE = 0.36 \pm 0.04$, $RMSE = 0.53 \pm 0.05$. These metrics reflect a solid correlation between experimental and predicted values (Figure 2).

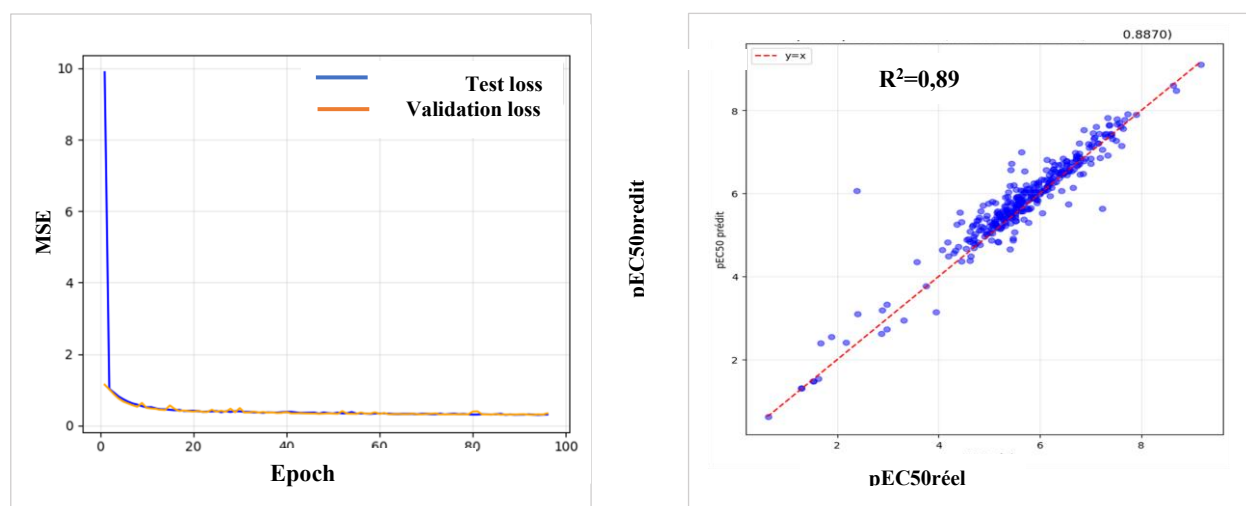


Figure 2: Loss and correlation graph

2. Validation on Reference FXR Agonists

Table 1 : Validation on reference FXR agonists

Agonist	Real pEC_{50}	Predicted pEC_{50}	Ratio (Predicted/Real)
GW4064	7.4	5.83	0.79
Obeticholic acid	7.00	5.48	0.79
Tropifexor	9.70	7.15	0.74
Cilofexor	7.3	5.74	0.79

To assess the model's generalizability, four well-characterized FXR agonists—GW4064, obeticholic acid (OCA), tropifexor, and cilofexor—were used as external validation compounds. The obtained predictions (predicted pEC_{50}) were compared to experimental values from the literature (Table 1) ²⁸. Although absolute predictions slightly underestimate experimental values (average ratio ≈ 0.8), the activity hierarchy is correctly preserved, with tropifexor remaining the most potent agonist. This relative consistency confirms the model's ability to identify and prioritize high-activity candidates, even with a slight absolute shift in values.

3. Selection of Drug Candidates and ADMET Filtering

Virtual screening of over one million molecules from PubChem, followed by multi-criteria filtering ($pEC_{50} \geq 7$,

QED > 0.6, Lipinski compliance), identified 694 potential candidates. After ADMET property evaluation using ADMETlab 3.0²⁹, nine molecules met the safety, bioavailability, and solubility conditions. Key parameters retained for NASH included: potency ($pEC_{50} > 7.1$), low hepatotoxicity (DILI < 0.2), low cardiac risk (hERG < 0.2), high oral bioavailability (<50%), acceptable solubility ($\log S > -5$). Nine molecules, M1(CID:8888557), M2(CID:22216658), M3(CID:8422059), M4(CID:7190756), M5(CID:18163764), M6(CID:8422070), M7(CID:10494847), M8(CID:84221227), M9(CID:7190831), were selected, and their pharmacokinetic and ADMET profiles are presented in the table 2.

Table 2: Some parameters allow for 09 filtered molecules

Parameter	M1	M2	M3	M4	M5	M6	M7	M8	M9
pEC_{50}	7.713	7.546	7.452	7.405	7.348	7.419	7.456	7.624	7.777
MW	348.20	364.24	364.24	348.20	375.25	350.22	306.16	406.25	321.16
QED	0.713	0.706	0.731	0.713	0.633	0.713	0.832	0.680	0.786
Lipinski	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Pfizer	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
GSK	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000
Caco-2	-5.106	-5.367	-5.242	-5.110	-5.361	-5.482	-5.265	-5.488	-5.155
PGP_inh	0.118	0.986	0.284	0.118	0.486	0.039	1.000	0.121	0.156
F50	0.960	0.997	0.997	0.917	0.942	0.656	0.875	0.793	0.453
BBB	0.267	0.000	0.183	0.101	0.270	0.074	0.000	0.259	0.152
PPB	88.847	82.725	49.580	83.997	87.391	79.259	69.499	49.642	84.215
CYP3A4-inh	0.054	0.295	0.983	0.993	0.986	0.999	0.504	0.991	0.683
$t_{1/2}$	0.650	0.592	0.385	0.628	0.458	0.623	0.886	0.384	0.660
hERG	0.162	0.033	0.055	0.087	0.082	0.054	0.038	0.102	0.060
DILI	0.147	0.067	0.094	0.153	0.034	0.055	0.153	0.158	0.149

QED Attractive: > 0.67; Lipinski (violation 1: yes, 0: no); Pfizer (Category 0: yes, 1: no); GSK (Category 0: yes, 1: no); Caco-2 (Optimal: > -5,15); PGP_inh (0: Non-inhibitor, 1: Inhibitor); F50 (1: <50% bioavailability, 0: $\geq 50\%$); BBB (1: BBB+, 0: BBB-); CYP3A4-inh (0: Non-inhibitor, 1: Inhibitor); $t_{1/2}$; hERG (1: $\geq 50\%$ hERG+, 0: <50% hERG-); DILI (1: High risk, 0: No risk).

The nine studied ligands exhibit activity values (pEC_{50}) ranging from 7.35 to 7.78, indicating a generally homogeneous and bioactive series against the FXR target. Among them, ligands M9 ($pEC_{50} = 7.78$) and M1 ($pEC_{50} = 7.71$) stand out as the most potent. All molecules comply with Lipinski's rule. The "drug-likeness" indices (QED) are high, ranging from 0.63 to 0.83, reflecting a favorable balance between size, polarity, and chemical complexity. Ligands M7 (0.83), M9 (0.79), and M3 (0.73) stand out as the most structurally optimized. No molecule shows Lipinski,

Pfizer, or GSK alerts, except for M8, which displays a positive GSK signal (1.0), indicating a possible reactive motif to monitor. Toxicological evaluation shows low probabilities of hERG channel blockage (0.03–0.16), ruling out major cardiotoxic risk. DILI (Drug-Induced Liver Injury) predictions also remain moderate (< 0.16). Integrating all these parameters, two profiles emerge (Figure3): molecule M9 combines high activity and excellent bioavailability. It is followed by M1, which also shows good activity but suffers from low bioavailability.

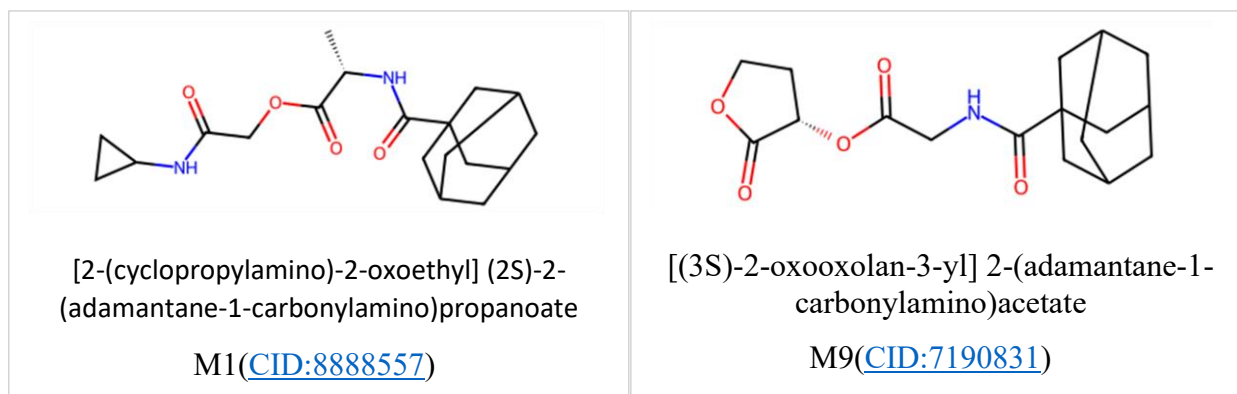


Figure 3: 2D Structure of M1 and M9 molecules

4. Molecular Docking and Interactions in the FXR Active Site

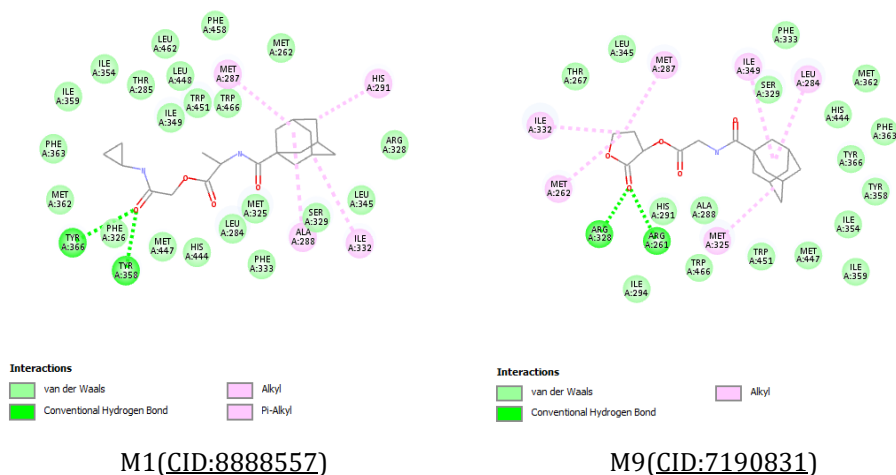


Figure 4: Interactions diagram of ligands M1 and M9 at the site of FXR (PDB : 10SV)

The molecular docking results (PDB ID: 10SV) reveal notable affinity differences among the studied compounds. Molecule M9 displays a score of -49.37 kcal/mol, compared to -49.11 kcal/mol for molecule M1, indicating markedly superior affinity of M9 for the FXR receptor. Ligands M1 and M9 establish a dense network of hydrophobic interactions and several hydrogen bonds within the FXR active site. Van der Waals interactions predominate with aliphatic and aromatic residues such as MET287, ILE332, ILE354, MET362, MET447, and PHE363, contributing to the stabilization of the complex's hydrophobic core. Additionally, hydrogen bonds with residues TYR358 and TYR366 for ligand M1, and with ARG261 and ARG328 for ligand M9, enhance their anchoring specificity. The slightly higher affinity observed for ligand M9 could be explained by the presence of its adamantyl group, which inserts deeply into the large hydrophobic pocket of the FXR active site, as well as by the reinforcement of π -alkyl interactions with residues ILE332, MET287, MET262, ILE349, and MET325 (Figure4).

DISCUSSION

In this study, we developed an integrative AI-assisted discovery pipeline combining a graph neural network model (GraphConvModel, $R^2 = 0.89$), molecular

screening, and docking. The model's use proved relevant in reproducing the activity hierarchy observed for reference FXR agonists such as GW4064, OCA, tropifexor, and cilofexor. These performances confirm the ability of graph neural networks to learn hierarchical molecular representations without resorting to manual descriptor engineering, thus offering a major advantage over conventional QSAR approaches. High-throughput virtual screening, in silico evaluation of ADMET properties, and molecular docking enabled the identification of new FXR agonists. Among the one million known molecules extracted from the PubChem database, two candidates, M1 (CID: 8888557) and M9 (CID: 7190831), stood out for their strong predicted affinity, favorable pharmacokinetic profile, and reduced toxicity.

1. Structural Analysis and Binding Interactions

The interaction profiles of M1 and M9 with the FXR LBD, as visualized in the docking outputs, reveal a conserved binding mode characterized by extended hydrophobic contacts and hydrogen bonds. Both ligands engage a network of hydrophobic contacts including residues ILE332, ILE359, LEU287, LEU349, MET262, MET287, MET362, PHE363, and SER329. Van der Waals interactions predominate with aliphatic residues (Ile, Leu, Met), stabilizing the hydrophobic core, while

conventional hydrogen bonds with polar residues (Arg, Tyr) anchor the ligands' polar groups, enhancing specificity³⁰ (Figure 5). These interactions align with crystallographic studies of FXR agonists, where bile acid

derivatives like chenodeoxycholic acid (CDCA) form similar networks, but the non-steroidal scaffolds of M1 and M9 offer reduced steric hindrance, potentially improving selectivity³¹.

2. Comparative Evaluation of Pharmacokinetic and ADMET Parameters

Table 3 : Comparative profile of FXR agonists OCA, Tropifexor, M1, and M9 according to pharmacokinetic and toxicological parameters

Parameter	OCA	Tropifexor	M1	M9
QED	0.577	0.21	0.713	0.786
Lipinski (violation)	0	1.0	0	0
LogS (solubility)	-4.69	-5.987	-3.069	-3.232
Caco-2	-5.391	-4.843	-5.106	-5.155
PPB (%)	95.753	99.051	88.847	84.215
BBB	0.0	0.264	0.267	0.152
F50 (ADMETlab 3.0)	0.51	0.993	0.960	0.453
DILI	0.183	1.0	0.147	0.149
hERG	0.01	0.898	0.162	0.06
CYP3A4-inh	1.0	0.0	0.054	0.683

The *in silico* evaluation of FXR agonists OCA, Tropifexor, M1, and M9 according to pharmacokinetic and toxicological highlights major differences between the compounds (Table 3).

The ADMET evaluation highlights that ligands M1 and M9 exhibit predicted pharmacokinetic and safety properties superior to those of tropifexor, while approaching the profile of OCA. M9 stands out as the best overall compromise, combining high drug-likeness, adequate solubility, moderate bioavailability, and low predicted toxicity. M1, on the other hand, shows excellent chemical stability and low toxicity, but its bioavailability requires adapted formulation strategies.

3. Mechanistic and Therapeutic Implications

The retained molecules both feature an adamantyl group (a tricyclic lipophilic structure). This is a key structural motif frequently used in medicinal chemistry.

It is often incorporated into sEH inhibitors (sEHIs), such as urea derivatives, to enhance their potency by facilitating favorable hydrophobic interactions with the sEH binding pocket³². Studies have explored compounds targeting both FXR and sEH. For example, Schmidt and collaborators developed an amide-based dual modulator of the FXR receptor and sEH to counter non-alcoholic steatohepatitis (NASH)³³. In this study, binding simulations show that ligands M1 and M9 stabilize the active agonist conformation of FXR. The Connolly surfaces of the ligands are shown in Figure 5. The adamantyl and cyclohexane groups contribute to an optimal balance between rigidity and lipophilicity, reducing steric constraints while maximizing contact surface with the large hydrophobic pocket of FXR³⁴. Thus, M1 and M9 could represent next-generation non-steroidal FXR agonists, likely to offer improved therapeutic efficacy and increased tolerance in NASH treatment.

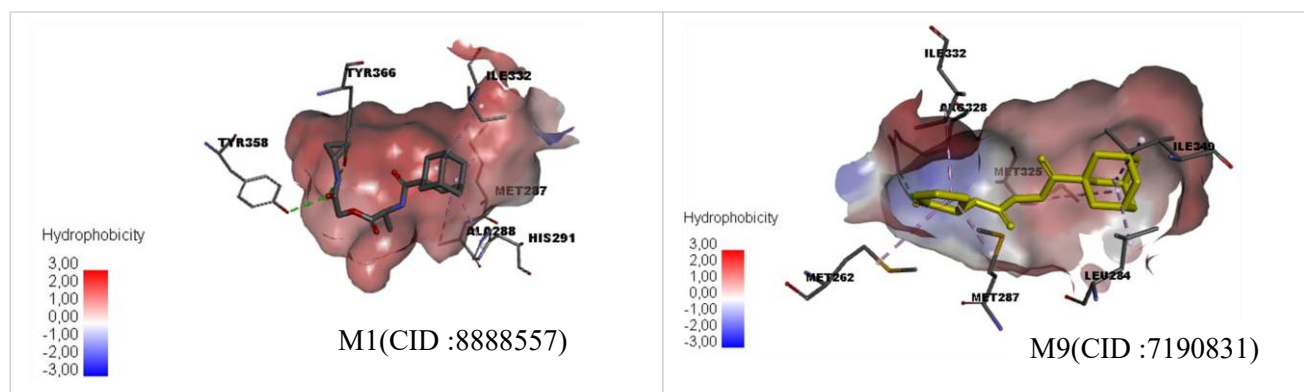


Figure 5: Connolly Surface of the active site of FXR for 2 best active designed molecules M1 and M9. The binding site surface is colored according to residue hydrophobicity: red = hydrophobic, blue = hydrophilic and white = intermediate

4. Limitations and Future Perspectives

Despite these advances, our study relies entirely on computational approaches, limited by the absence of experimental validation (e.g., in vitro assays on hepatic cells or murine NASH models). ADMET predictions and docking, while robust, may overestimate real affinity due to biases in databases (e.g., overrepresentation of bile acid scaffolds) or the lack of molecular dynamics simulations to assess complex stability³⁵. Additionally, GNNs, although performant, require larger datasets to minimize overfitting. In perspectives, chemical synthesis of M9 followed by preclinical assays is a priority, potentially possess favorable dual potency towards FXR and sEH while reducing the original cysteinyl leukotriene receptor antagonism of the lead drug³². This AI pipeline could be extended to other nuclear targets, accelerating the discovery of treatments for metabolic diseases.

CONCLUSION

This study highlights the relevance of an integrative approach combining artificial intelligence and molecular modeling for the discovery of new farnesoid X receptor (FXR) agonists in the context of metabolic-associated steatohepatitis (MASH, formerly NASH). The joint use of a neural predictive model (GraphConvModel), high-throughput virtual screening, and in-depth ADMET analysis has enabled the identification of two promising compounds, namely molecule M9 (CID: 7190831) and molecule M1 (CID: 8888557), which exhibit strong binding affinity, high oral bioavailability for M9, and low hepatic toxicity according to in silico predictions. The results of molecular docking on the FXR ligand-binding domain (PDB ID: 1OSV) revealed essential stabilizing interactions with residues PHE363, TYR358, and TRP451, involved in the stabilization of helix 12 and receptor activation. Among the tested compounds, M9 presents a denser interaction profile, suggesting superior agonist potential. In a rapidly evolving therapeutic landscape, marked by the FDA approval of resmetirom (THR- β agonist) in March 2024 for fibrosing MASH and the inconclusive evaluation for obeticholic acid, these non-steroidal candidates M1 and M9 offer a promising alternative, potentially in combination for multimodal therapies.

In perspective, M9 emerges as a priority candidate for chemical synthesis and experimental evaluation (in vitro and in vivo), in order to validate its efficacy against hepatic inflammation and fibrosis. More broadly, this integrated and reproducible computational pipeline illustrates AI's ability to accelerate the discovery of nuclear ligands, supporting the development of innovative metabolic therapies against MASH and other chronic liver diseases.

Conflict of Interest: The authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting this paper are available in the cited references.

Ethical approval: Not applicable.

REFERENCES

1. De A, Panigrahi M, Duseja A, Singh SP. Metabolic-dysfunction associated steatotic liver disease (MASLD). In: Hepatology. Elsevier; 2025:861-888. <https://doi.org/10.1016/B978-0-443-26711-6.00031-7>
2. Waheed A, Gul MH, Shabbir MUB, et al. FDA approves Resmetirom: groundbreaking treatment for NASH liver scarring in moderate to advanced fibrosis. *Annals of Medicine & Surgery*. 2025;87(3):1088-1091. <https://doi.org/10.1097/MS9.0000000000002770> PMID:40213239 PMCID:PMC11981246
3. Younossi ZM, Golabi P, De Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *Journal of Hepatology*. 2019;71(4):793-801. <https://doi.org/10.1016/j.jhep.2019.06.021> PMID:31279902
4. Azam MM, Mukhtar S, Haris M, et al. FDA's approval of resmetirom (Rezdiffra): a breakthrough in MASH management. *Explor Drug Sci*. Published online December 3, 2024:867-874. <https://doi.org/10.37349/eds.2024.00078>
5. Fahim SA, Attia YM, Messiha A, Nabawy AY, Refaat F, El-Maadawy WH. Comparative safety and side effects of semaglutide and tirzepatide: Implications for clinical decision-making in obesity management. *Biomedicine & Pharmacotherapy*. 2025;193:118731. <https://doi.org/10.1016/j.biopha.2025.118731> PMID:41177120
6. Adorini L, Trauner M. FXR agonists in NASH treatment. *Journal of Hepatology*. 2023;79(5):1317-1331. <https://doi.org/10.1016/j.jhep.2023.07.034> PMID:37562746
7. Chen M, Yang X, Lai X, Kang J, Gan H, Gao Y. Structural Investigation for Optimization of Anthranilic Acid Derivatives as Partial FXR Agonists by in Silico Approaches. *IJMS*. 2016;17(4):536. <https://doi.org/10.3390/ijms17040536> PMID:27070594 PMCID:PMC4848992
8. Saha A, Wood E, Omeragic L, et al. Farnesoid X Receptor (FXR) Agonists and Protein Kinase Regulation in NAFLD and NASH: Mechanisms and Therapeutic Potential. *Kinases and Phosphatases*. 2025;3(3):16. <https://doi.org/10.3390/kinasesphosphatases3030016>
9. Xiao H, Li P, Li X, et al. Synthesis and Biological Evaluation of a Series of Bile Acid Derivatives as FXR Agonists for Treatment of NASH. *ACS Med Chem Lett*. 2017;8(12):1246-1251. <https://doi.org/10.1021/acsmedchemlett.7b00318> PMID:29259742 PMCID:PMC5733277
10. Gohda K, Iguchi Y, Masuda A, Fujimori K, Yamashita Y, Teno N. Design and identification of a new farnesoid X receptor (FXR) partial agonist by computational structure-activity relationship analysis: Ligand-induced H8 helix fluctuation in the ligand-binding domain of FXR may lead to partial agonism. *Bioorganic & Medicinal Chemistry Letters*. 2021;41:128026. <https://doi.org/10.1016/j.bmcl.2021.128026> PMID:33839252
11. Tully DC, Rucker PV, Chianelli D, et al. Discovery of Tropifexor (LJN452), a Highly Potent Non-bile Acid FXR Agonist for the Treatment of Cholestatic Liver Diseases and Nonalcoholic Steatohepatitis (NASH). *J Med Chem*. 2017;60(24):9960-9973. <https://doi.org/10.1021/acs.jmedchem.7b00907> PMID:29148806
12. Edwards J, LaCerte C, Peyret T, et al. Modeling and Experimental Studies of Obeticholic Acid Exposure and the Impact of Cirrhosis Stage. *Clinical Translational Sci*. 2016;9(6):328-336.

- <https://doi.org/10.1111/cts.12421> PMID:27743502
PMCID:PMC5351006
13. NASH-Final-Report_Updated_011025.
14. Dufour JF, Anstee QM, Bugianesi E, et al. Current therapies and new developments in NASH. *Gut*. 2022;71(10):2123-2134. <https://doi.org/10.1136/gutjnl-2021-326874> PMID:35710299
PMCID:PMC9484366
15. Gupta R, Srivastava D, Sahu M, Tiwari S, Ambasta RK, Kumar P. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. *Mol Divers*. 2021;25(3):1315-1360. <https://doi.org/10.1007/s11030-021-10217-3> PMID:33844136
PMCID:PMC8040371
16. Gangwal A, Ansari A, Ahmad I, et al. Generative artificial intelligence in drug discovery: basic framework, recent advances, challenges, and opportunities. *Front Pharmacol*. 2024;15:1331062. <https://doi.org/10.3389/fphar.2024.1331062> PMID:38384298 PMCID:PMC10879372
17. Bechelli S, Delhommelle J. AI's role in pharmaceuticals: Assisting drug design from protein interactions to drug development. *Artificial Intelligence Chemistry*. 2024;2(1):100038. <https://doi.org/10.1016/j.aichem.2023.100038>
18. Jiménez J, Škalič M, Martínez-Rosell G, De Fabritiis G. KDEEP : Protein-Ligand Absolute Binding Affinity Prediction via 3D-Convolutional Neural Networks. *J Chem Inf Model*. 2018;58(2):287-296. <https://doi.org/10.1021/acs.jcim.7b00650> PMID:29309725
19. Kim S, Chen J, Cheng T, et al. PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Research*. 2021;49(D1):D1388-D1395. <https://doi.org/10.1093/nar/gkaa971> PMID:33151290
PMCID:PMC7778930
20. Dash RP, Babu RJ, Srinivas NR. Non-alcoholic Steatohepatitis (NASH) Drug Discovery - Building a Consensus on ADME Screening Tools and Clinical Pharmacology Strategies to Aid Candidate Development. *J Pharm Pharm Sci*. 2018;21:481-495. <https://doi.org/10.18433/jpps30022> PMID:30472977
21. <https://colab.research.google.com/>. Accessed November 2, 2025. <https://colab.research.google.com/>
22. visualise. Accessed October 28, 2025. <https://www.ebi.ac.uk/chembl/visualise>
23. Zdrazil B, Felix E, Hunter F, et al. The ChEMBL Database in 2023: a drug discovery platform spanning multiple bioactivity data types and time periods. *Nucleic Acids Research*. 2024;52(D1):D1180-D1192. <https://doi.org/10.1093/nar/gkad1004> PMID:37933841
PMCID:PMC10767899
24. Kearnes S, McCloskey K, Berndl M, Pande V, Riley P. Molecular graph convolutions: moving beyond fingerprints. *J Comput Aided Mol Des*. 2016;30(8):595-608. <https://doi.org/10.1007/s10822-016-9938-8> PMID:27558503 PMCID:PMC5028207
25. Zhang S, Tong H, Xu J, Maciejewski R. Graph convolutional networks: a comprehensive review. *Comput Soc Netw*. 2019;6(1):11. <https://doi.org/10.1186/s40649-019-0069-y> PMID:37915858 PMCID:PMC10615927
26. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*. 2012;64:4-17. <https://doi.org/10.1016/j.addr.2012.09.019>
27. Discovery Studio molecular modeling and simulation program version 2.5, Accelrys, Inc., San Diego, CA, 92121, USA, 2009.
28. Panzitt K, Zollner G, Marschall HU, Wagner M. Recent advances on FXR-targeting therapeutics. *Molecular and Cellular Endocrinology*. 2022;552:111678. <https://doi.org/10.1016/j.mce.2022.111678> PMID:35605722
29. <https://admetlab3.scbdd.com/>. Accessed November 2, 2025. <https://admetlab3.scbdd.com/>
30. Mane SA, Baka RL, Hatwar PR, Artificial Intelligence in Pharmaceutical Research, *Journal of Drug Delivery and Therapeutics*, 2025;15(6):260-267. <https://doi.org/10.22270/jddt.v15i6.7234>
31. Kydd-Sinclair D, Packer GL, Weymouth-Wilson AC, Watson KA. Structural Basis of Novel Bile Acid-Based Modulators of FXR. *Journal of Molecular Biology*. 2025;437(21):169383. <https://doi.org/10.1016/j.jmb.2025.169383> PMID:40803552
32. Das Mahapatra A, Choubey R, Datta B. Small Molecule Soluble Epoxide Hydrolase Inhibitors in Multitarget and Combination Therapies for Inflammation and Cancer. *Molecules*. 2020;25(23):5488. <https://doi.org/10.3390/molecules25235488> PMID:33255197 PMCID:PMC7727688
33. Schmidt J, Rotter M, Weiser T, et al. A Dual Modulator of Farnesoid X Receptor and Soluble Epoxide Hydrolase To Counter Nonalcoholic Steatohepatitis. *J Med Chem*. 2017;60(18):7703-7724. <https://doi.org/10.1021/acs.jmedchem.7b00398> PMID:28845983
34. Laboratoire de Physique Fondamentale et Appliquée (LPFA), University of Abobo Adjamé (now Nangui Abrogoua), Abidjan 02, Côte d'Ivoire, Banquet Okra GM, Brice D, N'Guessan H, Florance Kouassi A, Raymond KN. Conformational analysis and molecular design of anthranilic acid derivatives as partial agonists of the Farnesoid X Receptor (FXR) with favorable predicted pharmacokinetic profiles. *SDRP-JCCMM*. 2021;5(2):585-600. <https://doi.org/10.25177/JCCMM.5.2.RA.10760>
35. Wu N, Zhang R, Peng X, Fang L, Chen K, Jestilä JS. Elucidation of protein-ligand interactions by multiple trajectory analysis methods. *Phys Chem Chem Phys*. 2024;26(8):6903-6915. <https://doi.org/10.1039/D3CP03492E> PMID:38334015