Vantage: Journal of Thematic Analysis
(Vantage J. Them. Anal.) ISSN(E): 2582-7391 Vol. 7(1), April, 2026, 14-21

Original Research Article

Drug Repurposing of Metformin as a γ-Secretase Modulator in Cancer Therapy

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Received: 24/02/2026 | Accepted: 12/04/2026 | Published: 05/05/2026

ABSTRACT

A computational approach (in silico) combined with molecular docking, binding analysis, and interaction profiling was done to evaluate Metformin's affinity for the γ-secretase complex. Known γ-secretase binders, including Avagacestat, Semagacestat, Nirogacestat, and RO4929097,were used as positive controls for the comparative study and analysis of docking parameters. Metformin demonstrated an AC score of −205.66, with a moderate binding score of -4.56kcal/mol; despite its small size and hydrophilic nature, forming 3 stable hydrogen bonds with critical residues in the receptor's binding pocket. Comparison with established binders showed overlapping interaction sites, suggesting that Metformin could influence γ-secretase activity directly or indirectly. Assessment of hydrogen bonding and atomic contact scores further confirmed the stability and specificity of these interactions. This study highlights Metformin as a promising candidate for repurposing as an anticancer agent, potentially targeting both γ-secretase–Notch signaling and cancer metabolism. While the computational results provide strong preliminary evidence, further experimental validation in cell and animal models(*in-vitro*) is necessary to confirm the biological significance of these interactions. This work demonstrates the value of integrating computational and mechanistic approaches to identify new applications for existing drugs in cancer therapy.

Keywords: Metformin, γ-Secretase, Drug repurposing, cancer therapy, *in silico*

1. INTRODUCTION

Metformin, a first-line anti-diabetic drug (N,N-dimethylbiguanide), has gained attention for its potential anti-cancer properties (Žídek et al., 2024). As a safe, well-tolerated, and inexpensive therapy, Metformin's repurposing is appealing; epidemiological studies have reported reduced cancer incidence and mortality in diabetic patients taking Metformin (Rajale et al., 2026). Drug repurposing – using existing approved drugs for new indications – can dramatically shorten development time and cost (Pushpakom et al., 2019). In oncology, many approved drugs are being re-examined for anti-tumor activity (Biswas et al., 2013).

γ-Secretase is a multi-protein intramembrane protease complex (composed of presenilin, nicastrin, APH-1, and PEN-2) that cleaves various type-I transmembrane proteins including the Notch receptor, ErbB4, CD44, and cadherins (Wolfe, 2008).Gamma- secretase complex proteasome of the membrane is a type 1 transmembrane protein which is involved in introducing cleavage in other transmembrane protein/molecules/receptors. It is composed of 4 sub-units of proteins. The first one is Presenilin (PS1 or PS2) or the 'catalytic

core' which is involved in actual cleaving of the transmembrane. It has 2 aspartate residues (located on TM6 &TM7) that are involved in the aspartyl protease activity. Through γ-secretase cleavage, intracellular domains (ICDs) of these substrates are released to the nucleus to regulate gene transcription and cell fate (Fu et al., 2024). Notch signaling in particular is a key cell–cell communication pathway that drives proliferation and survival, and its dysregulation has been linked to many cancers (Shi et al., 2024). Indeed, elevated Notch-1 activity is observed in certain tumors and γ-secretase inhibitors (GSIs) that block Notch cleavage are under investigation as cancer therapies (Olsauskas-Kuprys et al., 2013).

Given Metformin's established metabolic effects on tumors and the central role of γ-secretase in oncogenic signaling, we explored the hypothesis that Metformin could bind to γ-secretase and modulate its activity. Here we report molecular docking of Metformin to the human γ-secretase complex, compared with several known GSIs (Semagacestat, Avagacestat, Nirogacestat, and RO4929097). We also assessed Metformin's predicted ADME/pharmacokinetic properties. This study assesses whether Metformin's binding affinity and drug-like profile support its repurposing as a γ-secretase-targeting agent in cancer.

2. MATERIALS AND METHODS

We performed structure-based docking of Metformin and control ligands against the human γ-secretase complex. The 2D structure of human gamma-secretase was retrieved from the Protein Data Bank (PDB ID:7C9I) and was used as the receptor, with preparation of the protein (removal of solvent, addition of hydrogens) via standard protocols. Ligand structures (Metformin and controls Avagacestat, Semagacestat, Nirogacestat, and RO4929097) were generated from SMILES or obtained from databases and parametrized with SwissParam.

Docking was performed using the SwissDock web service (EADock DSS engine) in the Attracting Cavities (AC) mode, which permits flexible ligand docking into protein cavities. The protein was prepared for molecular docking using mgltools (Kolpakov & Babaenko, 1998). The water molecules surrounding protein were deleted, kollman charges and polar hydrogen were added and protein file was saved in PDBQT format. The search grid encompassed the catalytic site of Presenilin. Multiple poses were generated and automatically clustered by SwissDock. Scoring parameters reported include the Binding score, AC score and SwissParam score. The AC score contains all energy contributions and is used to rank poses of the same ligand–target (more negative = better binding). The SwissParam score is an approximate binding free energy used to compare different ligand–target combinations. We selected the lowest (best) AC-score pose in the most populated cluster for each ligand. Hydrogen-bonding interactions between each ligand and γ-secretase residues were identified using molecular visualization software. The docked complexes were analysed using PyMOL (Yuan et al., 2017) and Ligplot (Wallace et al., 1995) for the interactions of docked poses of ligands with human γ-Secretase.

For pharmacokinetic profiling, we used SwissADME to predict drug-likeness, solubility, gastrointestinal absorption, blood–brain barrier (BBB) permeability, and P-glycoprotein (PGP) substrate status for Metformin. The SwissADME bioavailability radar and BOILED-Egg model were used to summarize Metformin's physicochemical and ADME characteristics. (Positive-control GSIs are known to have variable PK profiles; we focus on Metformin's profile here). All computational analyses follow best-practice docking and ADME-prediction workflows.

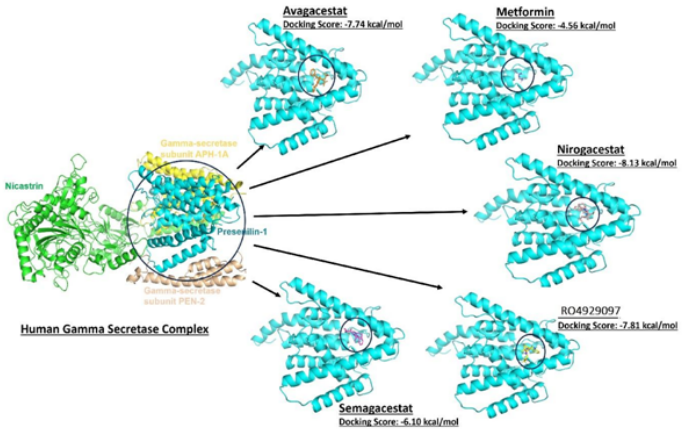

Figure 1: This figure shows the comparable binding of all the ligands to Presenilin-1, the catalytic-core of gamma secretase.

3. RESULTS

3.1 Molecular Docking

The docking yielded the following binding scores for metformin and controls (Table 1).

Metformin exhibited a very low (favorable) AC score (−205.66), indicating strong predicted binding affinity but with moderate binding score of -4.56kcal/mol. According to the AC score, Metformin is comparable to or better than that of semagacestat (−180.84) and significantly better than RO4929097 (−145.45). In contrast, avagacestat and nirogacestat showed weak AC scores (~−3.5), suggesting Metformin, though having a moderate binding affinity to the catalytic site, it still has other favourable scores to be considered for good binding parameters. The SwissParam scores are in a narrower range (−5.43 to −7.51); Metformin's SwissParam score (−6.43) is on par with the others as depicted in **Table 1.** **Figure 1** shows the comparable binding scores of all the ligands of γ-secretase with Presenilin-1 as the catalytic core which is the horseshoe-like structure, containing two active aspartate residues that cleave transmembrane domains of substrate proteins.

Hydrogen-bond interactions: Key hydrogen bonds were observed in the top docking pose of each ligand as shown in the Figure 2:

Table 1: Docking scores and interactions of ligands (Metformin, Avagacestat, Semagacestat, Nirogacestat, and RO4929097) with known γ-secretase.

Ligands	Docking score (kcal/mol)	AC Score	Swiss-Param Score
Met-formin	-4.56	-205.66	-6.43
Avagace-stat	-7.74	-3.41	-7.51
Sema-gacestat	-6.10	-180.89	-6.81
Nirogace-stat	-8.13	-3.51	-6.71
RO4929097	-7.81	-145.45	-5.43

- Metformin: 3 hydrogen bonds to Leu 432, Asp 385 and Asp 257on Presenilin-1
- Avagacestat: No hydrogen bonds
- Semagacestat: 2 hydrogen bondsat Lys 380 and Gly 382
- Nirogacestat: 1 hydrogen bond at Leu 432
- RO4929097: 4 hydrogen bonds at Asp 385, Lys 380, Leu 432 and Ala 434

Metformin's binding involved three strong hydrogen bonds with presenilin-1, whereas

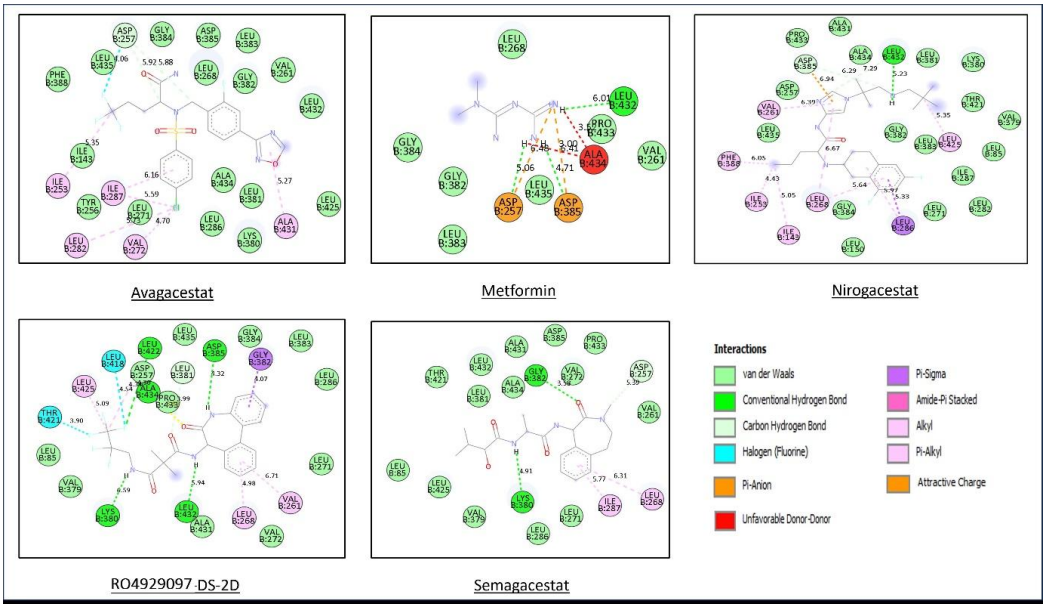

Figure 2: Two-dimensional (2D) structures of metformin and the control compounds selected for the study with human gamma-secretase.

Avagacestat, even with high binding score did not form any hydrogen bonds. However, Semagacestat and RO4929097 each formed 2 and 4 hydrogen bonds respectively, with catalytic-site residues. These interactions suggest Metformin occupies the GS active-site region comparably to known inhibitors.

ADME and pharmacokinetics: The SwissADME results in Figures3and 4 indicate that Metformin has favorable pharmacokinetic properties. Metformin is predicted to have high gastrointestinal (GI) absorption and moderate water solubility, but it does not cross the BBB. It satisfies all major drug-likeness rules (Kolpakov & Babaenko, 1998), with no violations. Notably, Metformin is predicted to be a P-glycoprotein (PGP) substrate (PGP negative), which may limit its brain exposure but can facilitate intestinal efflux. Metformin shows no inhibition of key CYP450 enzymes (CYP1A2, 2C19, 2C9, 2D6, 3A4), suggesting a low risk of metabolic drug–drug interactions. The bioavailability radar confirms that Metformin's size, polarity (TPSA $\approx$111 Å^2), and lipophilicity (consensus Log P $\approx$0.09) fall within optimal ranges for oral bioavailability. Overall, these data suggest Metformin's ADME profile is compatible with systemic administration and tumor exposure.

4. DISCUSSION

Our computational analysis suggests that Metformin binds strongly to the γ-secretase complex. The AC docking score of −205.66 for Metformin is notably favorable, exceeding that of the benchmark Semagacestat (−180.8) and RO4929097 (−145.5). The binding score though is moderate at -4.56kcal/mol, there are 3 strong hydrogen bonds implying that Metformin's predicted binding affinity is comparable to, or better than, some established GSIs. Metformin formed three key hydrogen bonds with presenilin-1 (to Leu 432, Asp 385 and Asp 257), anchoring it in the catalytic region. By contrast, some known GSIs (Avagacestat) showed poor docking here, consistent with their mixed clinical efficacy.

The favorable docking of Metformin aligns with emerging evidence that it can influence γ-secretase/Notch signaling (Jackson, 2025). For example, Metformin has been reported to inhibit Notch1 activity and suppress growth in mesothelioma and other cancer cells. Our findings support a molecular basis for this effect:

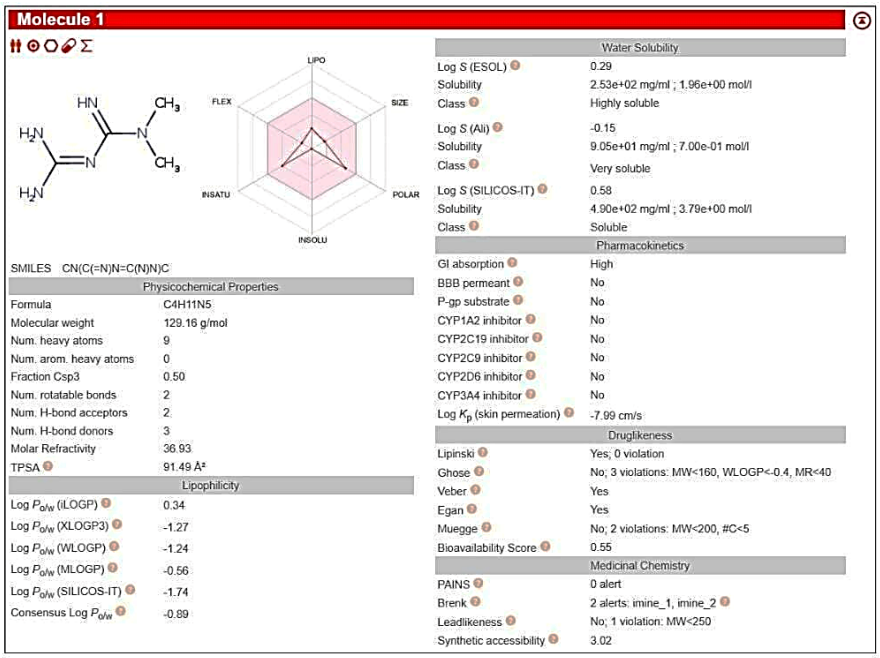

Figure 3: SwissADME profile for Metformin. The molecular property radar (red polygon) overlays ideal ranges (gray) for lipophilicity, size, polarity, solubility and saturation. Metformin falls largely within optimal ranges, indicating compliance with Lipinski, Ghose, Veber, Egan and Muegge drug-likeness rules. Key SwissADME predictions (side panels) include high water solubility (Log S > −2), no inhibition of major CYP enzymes, and a bioavailability score of 0.55. Metformin obeys Lipinski's rule of five and related filters, consistent with drug-like character.

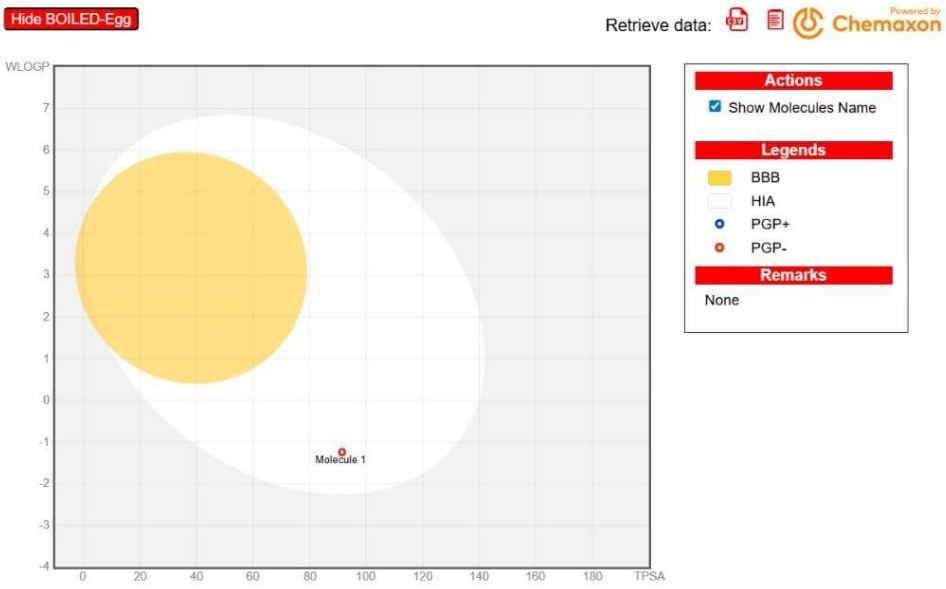

Figure 4: BOILED-Egg model for Metformin's absorption. The WLOGP–TPSA "Egg" diagram shows that Metformin (red dot) lies in the white (gastrointestinal absorption) region and outside the yellow yolk (BBB). This indicates high predicted GI absorption and negligible blood–brain barrier penetration. The legend indicates that Metformin is predicted to be a P-glycoprotein (PGP) substrate (red dot).

Metformin may directly occupy the γ-secretase active site, potentially interfering with Notch cleavage. γ-Secretase cleaves many oncogenic substrates (Notch, ErbB4, CD44, cadherins, etc.)

to release intracellular domains that drive tumorigenic transcriptional programs (Merilahti & Elenius, 2019). Inhibiting this protease with GSIs can block Notch signaling and has been explored in cancer therapy. That Metformin docks comparably to GSIs suggests it could contribute to Notch pathway inhibition, adding a novel dimension to its metabolic effects on cancer cells.

Importantly, Metformin's predicted pharmacokinetic properties differ substantially from those of classical γ-secretase inhibitors (GSIs). While *in silico* ADME profiling suggests acceptable systemic exposure, these models may not fully capture transporter-mediated distribution, particularly given Metformin's known dependence on organic cation transporters and its classification as a P-glycoprotein substrate. Its high GI absorption and lack of CYP inhibition suggest good systemic exposure without the complex metabolism of larger inhibitors. Being a known PGP substrate may limit tissue retention but is unlikely to preclude tumor uptake (McCaw et al., 2021). Consequently, intracellular accumulation at the γ-secretase complex remains uncertain. Its limited blood–brain barrier permeability may be advantageous for reducing central nervous system-related effects, although this is context-dependent and does not directly inform efficacy in peripheral tumors.

In contrast to GSIs, which have faced challenges related to off-target toxicity and limited selectivity, Metformin's established clinical safety profile and low cost are notable advantages. However, it is important to emphasize that the structural and physicochemical differences between Metformin and GSIs make direct functional equivalence unlikely, and any potential overlap in target engagement remains speculative.

There are several limitations to this study. Docking scores provide only an approximate estimate of binding affinity and do not demonstrate functional inhibition. Experimental validation is required to determine whether Metformin can directly interact with γ-secretase and modulate its enzymatic activity in biologically relevant systems. Additionally, γ-secretase processes multiple substrates, and nonspecific modulation may lead to complex and context-dependent biological effects.

While Metformin's role in activating AMP-activated protein kinase (AMPK) and altering cellular metabolism is well established, any additional impact on γ-secretase/Notch signaling remains hypothetical. However, in a review by Ikhlas & Ahmad (2017), Metformin has been shown to induce anticancer effects via both AMPK dependent and AMPK independent mechanisms by suppressing of mTORC1 signaling. mTORC1 is involved in cell growth, proliferation, protein synthesis and also regulate autophagy and apoptosis, thus inhibiting this signaling pathway has direct implications ontumor suppressive mechanisms. Future studies should therefore assess whether these pathways intersect under physiologically relevant conditions, and whether any combined effects contribute meaningfully to anticancer activity.

5. CONCLUSION

In summary, the docking and ADME analyses support the concept of repurposing Metformin as a γ-secretase-targeting agent in oncology. Metformin showed strong predicted binding to γ-secretase, with hydrogen bonding interactions comparable to known γ-secretase inhibitors. Its pharmacokinetic properties are compatible with systemic therapy. These findings suggest that Metformin may modulate cancer-related γ-secretase signaling pathways (e.g. Notch) in addition to its metabolic effects. Given Metformin's safety and affordability, our results warrant experimental follow-up: biochemical assays of γ-secretase activity and *in vitro* cancer studies combining Metformin with GSIs. If validated, Metformin repurposing could open a

novel avenue for cancer therapy, especially in Notch-driven tumors.

In summary the docking and ADME analyses suggest the potential feasibility of repurposing Metformin as a modulator of γ-secretase activity in oncology. Metformin demonstrated predicted binding interactions with γ-secretase, including possible hydrogen bonding patterns that partially overlap with those reported for established γ-secretase inhibitors. Its pharmacokinetic profile remains consistent with systemic administration; however, these predictions do not account for intracellular target accessibility or effective concentrations at the enzyme site.

Importantly, the relatively small size and physicochemical properties of Metformin differ substantially from classical γ-secretase inhibitors, and therefore its predicted binding should be interpreted with caution. While these findings raise the possibility that Metformin could influence γ-secretase-mediated signaling pathways, such as Notch, this effect remains hypothetical and requires rigorous validation.

Future work should focus on direct biochemical assays to evaluate γ-secretase activity in the presence of Metformin, followed by cell-based studies to assess any modulation of Notch signaling and cancer-relevant phenotypes. Overall, this study provides a preliminary computational basis for further investigation, rather than definitive evidence of γ-secretase inhibition by Metformin.

Conflict of Interest The authors have no financial or professional conflict of interest.

Funding

The authors received no financial assistance from any funding agency.

Acknowledgement

The authors thank the Principal, Hindu college, University of Delhi, and the Principal, Daulat Ram College, University of Delhi for support and guidance. The authors also thank DBT Star College Scheme granted to Hindu College, University of Delhi for logistics support.

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HOW TO CITE?

Harshit Narang, et al. (2026). Drug Repurposing of Metformin as a γ-Secretase Modulator in Cancer Therapy. *Vantage: Journal of Thematic Analysis*, 07(01), 14-21. https://vantagejournal.com/