AJPAM Reports
African Journal of Pharmacy and Alternative Medicine

https://doi.org/10.58460/ajpam.v5i03.249

RESEARCH ARTICLE

Computational Analysis of Fluoxetine, Gabapentin and Simvastatin ZINC Analogues for Neurogenesis Induction Activity in Ischemic Stroke

Odhiambo K. TREVOR*[1] & Njung'e R. KAGIA[1]

Author Affiliation(s)

1 Department of Clinical Pharmacy and Pharmacology, School of Pharmacy, Kabarak University.

*Corresponding Author: kennedytrevor332@gmail.com

To read this paper online, please scan the QR code below:

Submitted: 4th July 2026 | Accepted: 28th September 2026 | Published Online: 2nd November 2026

ABSTRACT

Stroke causes substantial mortality and disability, and current treatments leave a need for approaches supporting brain repair. Neurogenesis-related pathways provide potential targets, but the activity and safety of candidate compounds require rigorous evaluation using complementary computational and experimental approaches. This study compared fluoxetine, gabapentin and simvastatin with selected ZINC analogues to prioritise compounds for experimental investigation of neurogenesis-related activity after ischaemic stroke.This in-silico study combined ligand-based screening, molecular docking, pharmacokinetic prediction and toxicity prediction. SwissSimilarity identified 233 fluoxetine analogues and 400 analogues each for gabapentin and simvastatin. ZINCPharmer provided 18 additional gabapentin candidates. Ligands were prepared and optimised before AutoDock Vina docking against the serotonin 1A receptor (5-HT1A), serotonin transporter (SERT), voltage-gated calcium-channel auxiliary subunit α2δ2, and peroxisome proliferator-activated receptor alpha (PPAR-α), with parent drugs as comparators. Two docking runs per ligand–target pair used exhaustiveness 8. SwissADME and ProTox-III predicted pharmacokinetic and toxicological profiles.ZINC000012922723 produced more favourable docking scores than fluoxetine at both 5-HT1A and SERT. ZINC000005029316 and ZINC67903067 achieved scores of −8.2 kcal/mol at α2δ2. ZINC000096085336 had the most favourable simvastatin-series docking score, although interaction patterns required binding-site verification. Fluoxetine analogues showed favourable predicted absorption and brain permeability but frequent CYP inhibition flags. Gabapentin analogues varied in predicted permeability and synthetic accessibility. Toxicity flags across the series prevented conclusions of overall safety.ZINC000012922723 and ZINC000005029316 are priority candidates for experimental evaluation based on the combined computational results. Docking and predicted disposition do not establish neurogenic efficacy or safety. Target-specific docking validation, functional assays and experimental pharmacokinetic and toxicity studies are needed before therapeutic conclusions can be drawn.

Keywords: *Molecular Docking Simulation; Drug Discovery; Blood-Brain Barrier; Pharmacokinetics; Drug Repositioning.*

How to Cite this Article: TREVOR, O. K., & KAGIA, N. R. (2026). Computational Analysis of Fluoxetine, Gabapentin and Simvastatin ZINC Analogues for Neurogenesis Induction Activity in Ischemic Stroke. *African Journal of Pharmacy and Alternative Medicine*, 5(03), 350–359. https://doi.org/10.58460/ajpam.v5i03.249

This open access article is published by MJ&M Biolabs, Kenya © 2026 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC- BY-NC-SA) license.

INTRODUCTION

Stroke is a major cause of mortality and disability worldwide (Pacheco-Barrios et al., 2022). In Africa, 17.3 million disability-adjusted life years were lost to stroke in 2021, highlighting the need for effective and accessible interventions (Avan et al., 2025). Ischaemic stroke results from interruption of cerebral blood flow and accounts for most stroke cases. Its burden is particularly high in low- and middle-income countries (Kuriakose & Xiao, 2020).

Cerebral ischaemia compromises oxygen and glucose delivery, depletes ATP and disrupts neuronal membrane potentials. Depolarisation, excessive glutamate release and calcium influx contribute to mitochondrial dysfunction, oxidative stress, inflammation and neuronal death (Andrew et al., 2022). Reperfusion treatments are constrained by timing, eligibility and access (Kuriakose & Xiao, 2020), motivating investigation of approaches that could support subsequent brain repair.

Adult neurogenesis has been reported in the human hippocampus (Eriksson et al., 1998). Following ischaemic injury, progenitor responses in the subventricular and subgranular zones offer a potential repair mechanism. However, poor survival, maturation and integration of newly generated neurons limit endogenous recovery (Nagase et al., 2023; Zhu et al., 2018). Pharmacological enhancement of these processes remains a research objective rather than an established consequence of receptor binding.

Gabapentin has been investigated for recovery-related effects involving the voltage-gated calcium-channel auxiliary subunit α2δ2 (Zhang et al., 2024). Fluoxetine has been linked to neurogenesis through serotonin 1A receptor (5-HT1A)-associated modulation of GSK-3β/β-catenin signalling (Hui et al., 2015). Statins, including simvastatin, have also been investigated in relation to peroxisome proliferator-activated receptor alpha (PPAR-α)-dependent neurotrophin expression (Roy et al., 2015). These findings motivate examination of related compounds, but do not establish that structural similarity or favourable docking predicts neurogenic activity.

Computational screening can prioritise compounds for subsequent assays by comparing predicted target interactions, pharmacokinetics and toxicity (Shaker et al., 2021). This study therefore compared fluoxetine, gabapentin and simvastatin with selected ZINC analogues using ligand-based screening, molecular docking, SwissADME and ProTox-III. The objective was to identify candidates for experimental evaluation of neurogenesis-related activity after ischaemic stroke, while identifying limitations in predicted brain penetration, metabolism and safety.

METHODS

The study used PubChem and PubChem Sketcher V2.4 for ligand structures, SwissSimilarity and ZINCPharmer for screening, Avogadro (RRID:SCR_015983) for optimisation, RCSB PDB (RRID:SCR_012820) and UniProt for target information, UCSF Chimera and AutoDock Vina for preparation and docking, BIOVIA Discovery Studio for interaction visualisation, SwissADME for pharmacokinetic predictions, and ProTox-III for toxicity predictions. The materials and tools are summarised in Appendix A, Table A1.

Study Design

An in-silico study design (Shaker et al., 2021), and a quantitative research methodology were employed for this study that was conducted in the School of Pharmacy, Kabarak University.

Ligand-based Virtual Screening

The Swiss Similarity online tool (SwissSimilarity) received the canonical smiles of gabapentin, fluoxetine, and simvastatin (that were obtained from PubChem) and screened for molecules that are similar to the input ligands. This screening process was performed on the extensive ZINC database (RRID:SCR_006082) which is embedded in SwissSimilarity. Gabapentin and simvastatin each returned 400 analogues, while 233 analogues were identified for fluoxetine.

The canonical smiles of all the analogues (1,033) and the three parent drugs were then sketched, "cleaned," and the resulting structures downloaded as MDL molfiles using the PubChem sketcher program (PubChem Sketcher V2.4). The compounds and their analogues were translated to a three-dimensional format in the Avogadro software after which they were optimised using MMFF94s as the force field of choice, then saved in the Sybyl Mol2 file format.

ZINCPharmer was also used for ligand-based virtual screening of gabapentin analogues. No experimentally resolved gabapentin-bound α2δ2 structure was located for this study. The gabapentin-bound CaV1.2 complex PDB 8FD7 (Chen et al., 2023) was therefore used as an α2δ1-based surrogate template for pharmacophore generation, separately from the α2δ2 docking target. The deposited α2δ1 subunit is from rabbit (Oryctolagus cuniculus; label chain A, author chain D); the complex contains human and rabbit subunits and was expressed in human cells.

The complex was located using a calcium-channel search. The protein and bound gabapentin were separated using UCSF Chimera, saved in PDB format and loaded into ZINCPharmer. The 18 returned compounds were downloaded and subjected to target-based screening against α2δ2.

Target-based Virtual Screening

All compounds retrieved from SwissSimilarity (233 fluoxetine, 400 gabapentin and 400 simvastatin analogues) and ZINCPharmer (18 additional gabapentin candidates) underwent target-based virtual screening. Selection for subsequent pharmacokinetic and toxicity profiling was based on the most favourable (most negative) docking scores within each parent-drug series. Thus, selection for profiling occurred after docking of the complete retrieved sets. The 5-HT1A, SERT and PPAR-α target structures were obtained from RCSB PDB. The human (Homo sapiens) α2δ2 docking target was obtained through the UniProt entry Q9NY47 after following a target link from the DrugBank gabapentin record. This target-docking workflow was distinct from the α2δ1–gabapentin complex (PDB 8FD7) workflow used for ZINCPharmer screening. UCSF Chimera (RRID:SCR_004097) was used to remove non-standard residues, and the prepared targets were saved in PDB format. Docking was performed with AutoDock Vina (RRID:SCR_011958), following Eberhardt et al. (2021) and Trott & Olson (2010). Parent drugs were docked as comparators. Docking scores were recorded, and selected ligand–target interactions were visualised using BIOVIA Discovery Studio (RRID:SCR_015651).

To support reproducibility, the docking search box used for each target was defined as follows. For fluoxetine and its analogues, docking to the 5-HT1A receptor was performed using a search box centred at x = 167.048, y = 173.291, z = 180.489, with dimensions of 62.9444 × 84.6441 × 113.75 Å; docking to the SERT receptor used a search box centred at x = -35.4609, y = -11.2037, z = 19.8323, with dimensions of 72.5617 × 64.8642 × 97.8004 Å. For gabapentin and its analogues, docking to the α2δ2 subunit used a search box centred at x = 6.95391, y = -19.5479, z = 9.48127, with dimensions of 141.581 × 96.5737 × 115.283 Å. For simvastatin and its analogues, docking to the PPAR-α receptor used a search box centred at x = 35.4227, y = 27.84, z = 30.685, with dimensions of 42.3619 × 49.2471 × 50.212 Å. Docking was performed with an exhaustiveness setting of 8 and two independent docking runs per ligand-target pair. The target identifiers were the 5-HT1A receptor (PDB: 8PJK), the SERT receptor (PDB: 5I6X), the α2δ2 subunit (UniProt: Q9NY47), and the PPAR-α receptor (PDB: 6KAX). The parent drug structures were retrieved using PubChem CID 3386 (fluoxetine), CID 3446 (gabapentin), and CID 54454 (simvastatin).

Pharmacokinetic Analysis

The SwissADME online tool was used to forecast the pharmacokinetic characteristics of the drugs, and their analogues. The compounds' canonical smiles were fed into the tool, and the results exported in table format. Parameters such as molecular weight, log P, sensitivity to p-glycoprotein efflux, gastrointestinal absorption, blood–brain barrier permeability, conformity to Lipinski's rules, synthetic accessibility scores, and interactions with the cytochrome P450 enzymes were recorded.

Toxicity Analysis

To predict the toxicity of the drugs and their analogues, the ProTox III server tool (ProTox-III) was utilised. This was achieved through pasting the compounds' canonical smiles into the server and letting it make the toxicity predictions. Measures of toxicity such as Lethal Dose (LD50), toxicity class, as well as organ toxicity were the end results of this process.

Ethical Consideration

Ethical approval was sought from Kabarak University Institutional Scientific and Ethics Review Committee under approval number KUREC-040325. Additionally, a permit to conduct research was secured from the National Commission for Science, Technology and Innovation (NACOSTI) with licence number: NACOSTI/P/25/4175901. No consent for participation was required as the study was purely in-silico.

RESULTS

Docking scores and similarity indices are consolidated in Table 1. ZINC000012922723 tied with ZINC000084553549 for the most favourable 5-HT1A score (−10.5 kcal/mol) and had the most favourable SERT score (−10.7 kcal/mol), despite the lowest reported similarity index (70.1%). ZINC000005029316 and ZINC67903067 gave the most favourable gabapentin-series score (−8.2 kcal/mol). ZINC000096085336 had the most favourable simvastatin-series score. Similarity indices were unavailable for ZINCPharmer candidates because that screening used pharmacophore alignment.

Table 1: *Similarity Indices and Docking Scores of Parent Drugs and Selected ZINC Analogues*

	Fluoxetine	ZINC000012922723	ZINC000084555549	ZINC000012814	ZINC000009050	ZINC000030937
Similarity Index		0.701	0.837	0.836	0.845	0.831
Docking Scores (kcal/mol)	-7.6	-10.5	-10.5	-10.3	-10.3	-10.1
	-7.8	-10.7	-10.5	-10.2	-10	-10.5

	Gabapentin	ZINC000005029316	ZINC000004958052	ZINC000100245487	ZINC000257350276	ZINC67903067	ZINC27520768	ZINC72399925
Similarity Index		0.974	0.999	0.998	0.966			
Docking Scores (kcal/mol)	-5.3	-8.2	-7.1	-7	-7.9	-8.2	-8	-8

	Simvastatin	ZINC000096085336	ZINC000026182770	ZINC000085636470	ZINC000034109737	ZINC000034649840
Similarity Index		0.926	1	0.936	0.934	0.934
Docking Scores (kcal/mol)	-6.6	-8.1	-8	-7.8	-7.8	-7.8

Fluoxetine and its selected analogues had high predicted gastrointestinal absorption and blood–brain barrier permeability. All except ZINC000084553549 had no Lipinski violations. CYP2D6 and CYP3A4 inhibition was predicted throughout the series, and ZINC000012922723 and ZINC000012814358 were predicted P-glycoprotein substrates. No hepatotoxicity, mutagenicity or cytotoxicity was predicted, but blood–brain barrier and respiratory toxicity flags were present (Table 2).

Note: Docking scores are reported in kcal/mol; more negative values indicate more favourable predicted docking. Similarity indices are dimensionless. Blank similarity-index cells for ZINC67903067, ZINC27520768 and ZINC72399925 indicate that this measure was not available because these compounds were retrieved by ZINCPharmer pharmacophore screening. Parent-drug similarity-index cells are not applicable.

Interaction visualisations are provided in Appendix A, Figures S1–S9. Van der Waals, hydrogen-bonding, alkyl and halogen interactions varied by compound and target. PPAR-α interactions lacked a consistently conserved residue across the reported analogue series.

Table 2: *Predicted Pharmacokinetic and Toxicological Profiles of Fluoxetine and Selected Analogues*

	Fluoxetine	ZINC000012922723	ZINC000084555549	ZINC000012814358	ZINC000009050561	ZINC000030937300
Lipinski's Violations	0	0	1	0	0	0
BBB Penetration	Yes	Yes	Yes	Yes	Yes	Yes
GI Absorption	High	High	High	High	High	High
P-gp Substrate	No	Yes	No	Yes	No	No
CYP1A2	Yes	No	No	No	No	No
CYP2C19	Yes	Yes	No	Yes	Yes	Yes
CYP2C9	No	Yes	Yes	No	No	No
CYP2D6	Yes	Yes	Yes	Yes	Yes	Yes
CYP3A4	Yes	Yes	Yes	Yes	Yes	Yes
Synthetic Accessibility	2.56	3.62	3.51	2.9	2.83	3.13
LD50 (Toxicity Class)	248 (3)	1,460 (4)	300 (3)	2,100 (5)	4,000 (5)	1,000 (4)
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Active (0.54)	Active (0.53)	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Active (0.69)	Inactive	Inactive	Inactive
BBB Toxicity	Active (0.99)	Active (0.82)	Active (0.94)	Active (0.89)	Active (0.89)	Active (0.92)
Respiratory Toxicity	Active (0.95)	Active (0.76)	Active (0.77)	Active (0.74)	Active (0.75)	Active (0.81)

The ZINCPharmer gabapentin analogues showed Lipinski violations and lacked predicted blood–brain barrier permeability, as did ZINC000257350276. Only ZINC67903067 had low predicted gastrointestinal absorption. ZINC27520768 was the only candidate with CYP inhibition flags, involving CYP2C19 and CYP2C9. Toxicity predictions varied, including hepatotoxicity for ZINC27520768 and toxicity class 3 for ZINC72399925 (Table 3).

Table 3: *Predicted Pharmacokinetic and Toxicological Profiles of Gabapentin and Selected Analogues*

	Gabapentin	ZINC000000050	ZINC000000049	ZINC000001002	ZINC000002573	ZINC6790306	ZINC2752076	ZINC7239992
Lipinski's Violations	0	0	0	0	0	3	1	1
BBB Penetration	Yes	Yes	Yes	Yes	No	No	No	No
GI Absorption	High	High	High	High	High	No	High	High
P-gp Substrate	No	Yes	Yes	Yes	Yes	Yes	No	No
CYP1A2	No	No	No	No	No	No	No	No
CYP2C19	No	No	No	No	No	No	Yes	No
CYP2C9	No	No	No	No	No	No	Yes	No
CYP2D6	No	No	No	No	No	No	No	No
CYP3A4	No	No	No	No	No	No	No	No
Synthetic Accessibility	1.63	4.21	4.23	3.88	4.86	8.21	3.18	7.96
LD50 (Toxicity Class)	10,000 (6)	3,400 (5)	10,000 (6)	10,000 (6)	6,900 (6)	4,000 (5)	1,120 (4)	260 (3)
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Active (0.53)	Inactive
Carcinogenicity	Active (0.53)	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Inactive	Inactive	Active (0.99)	Active (0.99)	Active (0.97)	Active (0.99)
BBB Toxicity	Active (0.95)	Active (0.73)	Active (0.93)	Active (0.86)	Active (0.64)	Active (0.57)	Active (0.65)	Inactive
Respiratory Toxicity	Active (0.94)	Active (0.88)	Active (0.78)	Active (0.69)	Active (0.74)	Active (0.60)	Inactive	Active (0.88)

Simvastatin and its selected analogues were predicted to have high gastrointestinal absorption and no Lipinski violations. Blood–brain barrier permeability was predicted for simvastatin and all listed analogues except ZINC000026182770. P-glycoprotein and CYP inhibition predictions varied (Table 4). No hepatotoxicity, mutagenicity or cytotoxicity was predicted, but other toxicity flags preclude an overall safety conclusion.

Table 4: *Predicted Pharmacokinetic and Toxicological Profiles of Simvastatin and Selected Analogues*

	Simvastatin	ZINC000096085336	ZINC000026182770	ZINC000085636470	ZINC000034109737	ZINC000034649840
Lipinski's Violations	0	0	0	0	0	0
BBB Penetration	Yes	Yes	No	Yes	Yes	Yes
GI Absorption	High	High	High	High	High	High
P-gp Substrate	No	No	No	No	Yes	Yes
CYP1A2	No	No	No	No	No	No
CYP2C19	No	No	No	No	No	No
CYP2C9	Yes	No	No	No	Yes	Yes
CYP2D6	No	No	No	No	No	No
CYP3A4	Yes	No	Yes	No	Yes	Yes
Synthetic Accessibility	5.8	4.64	5.74	4.64	5.72	5.72
LD50 (Toxicity Class)	1,000 (4)	1,330 (4)	8,939 (6)	1,330 (4)	3,000 (4)	3,000 (4)
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Active (0.64)	Active (0.50)	Active (0.74)	Active (0.50)	Active (0.54)	Active (0.54)
Mutagenicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Active (0.99)	Inactive	Active (0.99)	Inactive	Inactive	Inactive
BBB Toxicity	Active (0.98)	Active (0.82)	Active (0.68)	Active (0.82)	Active (0.89)	Active (0.89)
Respiratory Toxicity	Active (0.96)	Active (0.57)	Active (0.96)	Active (0.57)	Inactive	Inactive

Chemical structures are provided in Appendix A, Figures S10–S18. Fluoxetine analogues contained aromatic and trifluoromethyl groups with altered linkages. Gabapentin analogues included bulkier steroid-like or aromatic structures.

DISCUSSION

Several analogues produced more favourable docking scores than their parent drugs, supporting their prioritisation for experimental evaluation rather than demonstrating neurogenesis. ZINC000012922723 improved on fluoxetine's score by 2.9 kcal/mol at both 5-HT1A and SERT. ZINC000005029316 and ZINC67903067 improved on gabapentin by 2.9 kcal/mol at α2δ2, while ZINC000096085336 improved on simvastatin by 1.5 kcal/mol at PPAR-α (Table 1). Comparisons are within each target and scoring protocol; scores do not establish functional activity or clinical efficacy.

The fluoxetine analogues replace or supplement the parent drug's ether linkage with amide linkages, which may alter hydrogen-bonding opportunities. Bulkier, more rigid gabapentin analogues may make additional receptor contacts, although docking alone cannot establish the contribution of these features. The chemical structures are presented in Appendix A, Figures S10–S18.

At 5-HT1A, fluoxetine and the selected analogues shared van der Waals contacts with phenylalanine 112 and alkyl interactions with isoleucine 189. At SERT, glycine 498 participated in van der Waals interactions across the series, while halogen interactions varied between compounds. Gabapentin (Figure S5) and ZINC67903067 (Figure S7) shared hydrogen bonding with arginine 791 and van der Waals interactions with asparagine 540. ZINC000005029316 is a different analogue, illustrated in Figure S6; its displayed contacts include glutamate 917, histidine 805, arginine 913 and glutamine 1017. These differ from the contacts displayed for gabapentin in Figure S5. Both figures represent docking at α2δ2. Gabapentin and ZINC000005029316 each showed unfavourable acceptor–acceptor interactions, but different receptor residues were involved. The distinct contact patterns suggest that ZINC000005029316 may occupy a different binding region from gabapentin and ZINC67903067. This raises a hypothesis of alternative binding regions on α2δ2, requiring coordinate alignment, consistent residue mapping and pose validation; the interaction diagrams alone do not establish two functional binding pockets or explain the score difference. Appendix A, Figures S1–S9 retain the detailed interaction visualisations.

Sudhakar et al. (2025) similarly reported ligands with more favourable scores than fluoxetine against SERT structure 5I6X using Glide XP. This provides a related screening comparison, but agreement between studies using different docking engines does not validate the present poses or scores.

Use of the α2δ1-derived pharmacophore was motivated by gabapentin recognition by both α2δ1 and α2δ2 (Marais et al., 2001). Page et al. (2023) describe a conserved amino acid-binding pocket that accommodates gabapentinoids in both isoforms. Reported gabapentin dissociation constants of 59 nM for α2δ1 and 153 nM for α2δ2 nevertheless indicate different affinities (Marais et al., 2001). These findings support exploratory use of a surrogate geometry, but do not demonstrate pharmacophore transferability or improved binding to α2δ2.

Simvastatin analogues showed heterogeneous PPAR-α interaction patterns without a consistently conserved residue. This complicates interpretation of their improved docking scores and requires binding-site verification. Roy et al. (2015) linked statin activity in mice to PPARα-CREB signalling and identified leucine 331 and tyrosine 334 as important interaction residues. Figure S9 shows a van der Waals contact with tyrosine 334 for ZINC000096085336; leucine 331 is not shown in that interaction diagram. A single shared residue does not establish an equivalent binding mode. Differences in species, structures or docking poses may contribute, but were not resolved in this study.

Predicted pharmacokinetic profiles identified further trade-offs (Tables 2–4). Fluoxetine analogues showed high gastrointestinal absorption and predicted blood–brain barrier permeability, but frequent CYP inhibition flags. ZINC000012922723 and ZINC000012814358 were also predicted P-glycoprotein substrates. These findings identify questions for transporter and metabolic assays rather than established drug interactions. Most gabapentin analogues lacked CYP inhibition predictions, although the ZINCPharmer candidates had Lipinski violations and predicted barriers to brain penetration. ZINC000257350276 also lacked predicted blood–brain barrier permeability, which limits its prioritisation for a central nervous system indication despite favourable docking.

Simvastatin analogues had broadly favourable absorption and permeability predictions, but the model predicted CYP3A4 inhibition for simvastatin itself. The prescribing information cited in the manuscript instead describes simvastatin as a CYP3A4 substrate without CYP3A4 inhibition (FDA & Merck & Co., 2015). This discrepancy illustrates why the computational outputs require experimental confirmation. Synthetic accessibility scores also inform prioritisation, with ZINC67903067 and ZINC72399925 presenting greater predicted synthesis difficulty than most candidates.

Predicted parent-drug LD50 values were 10,000 mg/kg for gabapentin, 1,000 mg/kg for simvastatin and 248 mg/kg for fluoxetine. These model estimates do not establish overall clinical safety. Blood–brain barrier and respiratory toxicity flags occurred across many compounds. The cited clinical literature does not establish routine blood–brain barrier toxicity for these parent drugs: de Oliveira (2016) describes other fluoxetine adverse effects, while Liu et al. (2024) discuss statin-associated barrier protection. Respiratory adverse effects have been discussed for gabapentin (Quintero, 2017), simvastatin (Jessurun et al., 2021) and antidepressants including fluoxetine (Shooshtari et al., 2025). Such reports provide context but do not validate compound-specific predictions or their probabilities.

The absence of predicted hepatotoxicity, mutagenicity or cytotoxicity in several series should not obscure other model flags. Carcinogenicity and immunotoxicity predictions warrant follow-up, particularly in the simvastatin series. Overall, ZINC000012922723 and ZINC000005029316 remain priority candidates for validation, while additional fluoxetine and gabapentin analogues require selection against permeability, metabolic and toxicity constraints. Simvastatin analogues were deprioritised because of uncertain binding-site correspondence and toxicity predictions.

LIMITATIONS

All findings were computational, with no experimental confirmation of binding, functional activity, neurogenesis, pharmacokinetics or toxicity. Reference-ligand redocking and pose RMSD validation were not performed for any target. General AutoDock Vina benchmarking (Trott & Olson, 2010; Eberhardt et al., 2021) does not substitute for study-specific validation. The human α2δ2 docking target was obtained through UniProt Q9NY47 via DrugBank, separately from the α2δ1–gabapentin complex 8FD7 used for pharmacophore screening. No experimentally resolved gabapentin-bound α2δ2 structure was located for this study. Using a rabbit α2δ1-based surrogate introduces cross-isoform and cross-species uncertainty; shared ligand recognition does not establish transferability to human α2δ2. The exact Q9NY47-linked coordinate-model identifier/version and the chain selection used during preparation remain incompletely documented. The proposed alternative α2δ2 binding regions require coordinate alignment, residue mapping and pose validation. Two docking runs per pair do not resolve these limitations. SwissADME and ProTox-III predictions may conflict with established parent-drug information. Binding-site validation, biochemical assays and neurogenesis models are needed before biological or therapeutic conclusions can be drawn.

CONCLUSION

The study identifies ZINC analogues with more favourable docking scores than their parent drugs, alongside differing predicted pharmacokinetic and toxicity profiles. ZINC000012922723 and ZINC000005029316 are priorities for experimental evaluation. Distinct α2δ2 contact patterns suggest a possible alternative binding region for ZINC000005029316, warranting structural and experimental investigation. Other fluoxetine and gabapentin analogues require further assessment of brain permeability, metabolic interactions and toxicity. Uncertain binding-site correspondence and toxicity predictions limit prioritisation of the simvastatin series. These findings guide experimental selection but do not demonstrate neurogenesis, clinical benefit or safety.

RECOMMENDATIONS

Researchers should first verify target structures and binding sites, perform reference-ligand redocking where suitable experimental complexes are available, and examine reproducibility of the leading poses. Binding and functional assays should precede neurogenesis studies. Candidate selection should then incorporate measured brain permeability, transporter effects, CYP inhibition and toxicity, with particular attention to computational flags and discrepancies involving the parent drugs.

DECLARATION

Availability of Data and Material

The datasets generated and/or analysed during this study are available at the Harvard repository, and can be accessed via: https://doi.org/10.7910/DVN/PAVNWR

Competing Interests

The authors declare that they have no competing interests.

Authors' Contribution

KT contributed to the conception, design, acquisition, analysis and interpretation of the study, drafted and critically revised the manuscript throughout the editorial process.
RK contributed to the conception, design, formatting, analysis and approval of the submitted version. Both authors accept accountability for all aspects of the work.

Funding

The study was funded equally by KT and RK. As author-funders, both contributed to study conception, design and analysis; KT drafted and critically revised the manuscript, and both approved the submitted version and jointly decided to publish.

Acknowledgements

The authors thank Dr. Filex Otieno for guidance on manuscript editing and addressing editorial requests, and Dr. Jewel Nungari for running the docking simulations for simvastatin and its analogues and providing moral support. Both agreed to be named. Neither served as a medical writer or received payment for these contributions.

REFERENCES

Andrew, R. D., Hartings, J. A., Ayata, C., Brennan, K. C., Dawson-Scully, K. D., Farkas, E., Herreras, O., Kirov, S. A., Müller, M., Ollen-Bittle, N., Reiffurth, C., Revah, O., Robertson, R. M., Shuttleworth, C. W., Ullah, G., & Dreier, J. P. (2022). The Critical Role of Spreading Depolarizations in Early Brain Injury: Consensus and Contention. Neurocritical Care, 37, 83–101. https://doi.org/10.1007/s12028-021-01431-w

Avan, A., Hachinski, V., Njamnshi, W. Y., Andersson, N., & Njamnshi, A. K. (2025). The burden of stroke, ischaemic heart disease, and dementia in Africa, 1990–2021: an ecological analysis of the Global Burden of Disease 2021. The Lancet Global Health, 13(7), e1191–e1202. https://doi.org/10.1016/S2214-109X(25)00109-3

Chen, Z., Mondal, A., & Minor, D. L., Jr. (2023). Structural basis for CaVα2δ:gabapentin binding. Nature Structural & Molecular Biology, 30, 735–739. https://doi.org/10.1038/s41594-023-00951-7

de Oliveira, M. R. (2016). Fluoxetine and the mitochondria: A review of the toxicological aspects. Toxicology Letters, 258, 185–191. https://doi.org/10.1016/j.toxlet.2016.07.001

Eberhardt, J., Santos-Martins, D., Tillack, A. F., & Forli, S. (2021). AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. Journal of Chemical Information and Modeling, 61(8), 3891–3898. https://doi.org/10.1021/acs.jcim.1c00203

Eriksson, P. S., Perfilieva, E., Björk-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A., & Gage, F. H. (1998). Neurogenesis in the adult human hippocampus. Nature Medicine, 4(11), 1313–1317. https://doi.org/10.1038/3305

FDA, & Merck & Co., Inc. (2015). FDA Prescribing Information for ZOCOR (Simvastatin) tablets. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/019766s093lbl.pdf

Hui, J., Zhang, J., Kim, H., Tong, C., Ying, Q., Li, Z., Mao, X., Shi, G., Yan, J., Zhang, Z., & Xi, G. (2015). Fluoxetine regulates neurogenesis in vitro through modulation of gsk-3b/b-catenin signaling. International Journal of Neuropsychopharmacology, 18(5), 1–12. https://doi.org/10.1093/ijnp/pyu099

Jessurun, N. T., Drent, M., Wijnen, P. A., Harmsze, A. M., van Puijenbroek, E. P., Bekers, O., & Bast, A. (2021). Role of Drug–Gene Interactions and Pharmacogenetics in Simvastatin-Associated Pulmonary Toxicity. Drug Safety, 44(11), 1179–1191. https://doi.org/10.1007/s40264-021-01105-8

Kuriakose, D., & Xiao, Z. (2020). Pathophysiology and treatment of stroke: Present status and future perspectives. International Journal of Molecular Sciences, 21(20), 1–24. https://doi.org/10.3390/ijms21207609

Liu, J. C., Lei, S. Y., Zhang, D. H., He, Q. Y., Sun, Y. Y., Zhu, H. J., Qu, Y., Zhou, S. Y., Yang, Y., Li, C., & Guo, Z. N. (2024). The pleiotropic effects of statins: a comprehensive exploration of neurovascular unit modulation and blood–brain barrier protection. Molecular Medicine, 30(1). https://doi.org/10.1186/s10020-024-01025-0

Marais, E., Klugbauer, N., & Hofmann, F. (2001). Calcium channel α2δ subunits-structure and gabapentin binding. Molecular Pharmacology, 59(5), 1243–1248. https://doi.org/10.1124/mol.59.5.1243

Nagase, T., Kin, K., & Yasuhara, T. (2023). Targeting Neurogenesis in Seeking Novel Treatments for Ischemic Stroke. Biomedicines, 11(10). https://doi.org/10.3390/biomedicines11102773

Pacheco-Barrios, K., Giannoni-Luza, S., Navarro-Flores, A., Rebello-Sanchez, I., Parente, J., Balbuena, A., de Melo, P. S., Otiniano-Sifuentes, R., Rivera-Torrejón, O., Abanto, C., Alva-Diaz, C., Musolino, P. L., & Fregni, F. (2022). Burden of Stroke and Population-Attributable Fractions of Risk Factors in Latin America and the Caribbean. Journal of the American Heart Association, 11(21), e027044. https://doi.org/10.1161/JAHA.122.027044

Page, K. M., Gumerov, V. M., Dahimene, S., Zhulin, I. B., & Dolphin, A. C. (2023). The importance of cache domains in α2δ proteins and the basis for their gabapentinoid selectivity. Channels, 17(1), 2167563. https://doi.org/10.1080/19336950.2023.2167563

Quintero, G. C. (2017). Review about gabapentin misuse, interactions, contraindications and side effects. Journal of Experimental Pharmacology, 9, 13–21. https://doi.org/10.2147/JEP.S124391

Roy, A., Jana, M., Kundu, M., Corbett, G. T., Rangaswamy, S. B., Mishra, R. K., Luan, C. H., Gonzalez, F. J., & Pahan, K. (2015). HMG-CoA Reductase Inhibitors Bind to PPARα to Upregulate Neurotrophin Expression in the Brain and Improve Memory in Mice. Cell Metabolism, 22(2), 253–265. https://doi.org/10.1016/j.cmet.2015.05.022

Shaker, B., Ahmad, S., Lee, J., Jung, C., & Na, D. (2021). In silico methods and tools for drug discovery. Computational Biology and Medicine, 137, 104851. https://doi.org/10.1016/j.compbiomed.2021.104851

Shooshtari, A. A., Jayaraman, E. A., Kesavan, R., Sarva, S., Manjunath, S., & Patel, A. (2025). Antidepressants and lung toxicity: A narrative review. Cureus, 17(8), e89263. https://doi.org/10.7759/cureus.89263

Sudhakar, N., Deepika, E. V., Negalya, S., & Ram Kumar, R. S. (2025). In-silico drug discovery of flavonoids targeting the human serotonin transporter: A multi-approach computational study for depression. International Journal of Pharmaceutical Sciences, 3(6), 1896–1921. https://doi.org/10.5281/zenodo.15629635

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, 31(2), 455–461. https://doi.org/10.1002/jcc.21334

Zhang, Y., Zhang, C., Yi, X., Wang, Q., Zhang, T., & Li, Y. (2024). Gabapentinoids for the treatment of stroke. Neural Regeneration Research, 19(7), 1509–1516. https://doi.org/10.4103/1673-5374.387968

Zhu, S. Z., Szeto, V., Bao, M. H., Sun, H. S., & Feng, Z. P. (2018). Pharmacological approaches promoting stem cell-based therapy following ischemic stroke insults. Acta Pharmacologica Sinica, 39(5), 695–712. https://doi.org/10.1038/aps.2018.23