RESEARCH PAPER

Design, Synthesis, and In Silico Evaluation of Novel Imidazolidine-2,4-dione Derivatives as Selective GSK-3β Inhibitors..

Amrita Singh[1], Ajay kumar[1*], Pankaj Singh Niranjan[2], Shashi Kiran Misra[1]

[1]*School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, Uttar Pradesh 208024, India*
Email : amritasingh@csjmu.ac.in, ajaykumar@csjmu.ac.in, shashikmishra@csjmu.ac.in
[2]*Institute of pharmacy, Bundelkhand University, Jhansi*
Email-drpankajniranjan@gmail.com

ABSTRACT
Diabetes mellitus (DM) is a lifelong metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global prevalence of DM is increasing at a frightening rate to over 783 million cases projected by 2045. Type 2 diabetes mellitus (T2DM), the most common form, is a companion of insulin resistance, glucose uptake defect, and impaired glycogen metabolism. Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase involved in the central regulation of insulin action by its phosphorylation and inhibition of glycogen synthase and, thus, in hyperglycemia. Inhibition of GSK-3 has been viewed as a therapeutic strategy to amplify insulin sensitivity and offer better Glycemic control.
The current research focuses on the synthesis and characterization of new imidazolidine-2,4-dione derivatives as prospective GSK-3 inhibitors. Two-step synthesis pathway was chosen starting from benzoyl chloride analogues which were treated with p-hydroxybenzaldehyde to give intermediate products, followed by condensation with hydantoin derivatives. Synthesized compounds were characterized through thin layer chromatography (TLC), melting point measurement, and spectroscopic analysis (IR, NMR, and mass spectrometry). Molecular docking experiments performed by AutoDock Vina were performed to ascertain binding capacity to GSK-3β. Some of the compounds possessed favorable binding scores, such as the o-phenyl, p-phenyl, and m-triethylammonium substituted compound, which shows great promise as GSK-3 inhibitors.
These findings point to imidazolidine-2,4-dione derivatives with selective aromatic and heterocyclic substitutions as good lead compounds for anti-diabetic drug research and development. Further studies in vitro and in vivo would be required to ascertain their pharmacological activity and safety profiles.
Keywords: Diabetes mellitus, GSK-3 inhibitors, Imidazolidine-2,4-dione, Hydantoin derivatives, Docking studies, Anti-diabetic drug design.
How to cite this article: Singh A, Kumar A, Niranjan PS, Misra SK; Design, Synthesis, and In Silico Evaluation of Novel Imidazolidine-2,4-dione Derivatives as Selective GSK-3β Inhibitors....Int J Drug Deliv Technol. 2026;16 (8s): 188-203; DOI: 10.25258/ijddt.16.8s.30
Source of support: Nil.
Conflict of interest: Nil.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic syndrome with chronic hyperglycemia caused by an insulin secretory defect, an insulin receptor or postreceptor defect, or both. It is also complicated by devastating microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (atherosclerosis, cardiovascular disease) complications responsible for most of the morbidity and mortality globally. Of the 537 million adults who had diabetes in 2021, as estimated by the International Diabetes Federation (IDF), it is expected to rise to 643 million by 2030 and 783 million by 2045. They predominantly reside in low- and middle-income nations, substantiating worldwide imbalance between diabetes burden and access to health care.
The most common type of diabetes is type 2 diabetes mellitus (T2DM), which is characterized by inadequate insulin-sensitive peripheral tissue utilization (i.e., skeletal muscle, adipose tissue, and liver), and inadequate insulin secretion by pancreatic β-cells to compensate for the insulin resistance. Chronic insulin resistance leads to reduced glucose utilization and increased hepatic glucose production, resulting in the persistence of hyperglycemia (high blood sugar). Multiple molecular mechanisms have been identified in T2DM pathophysiology, and among these, glycogen synthase kinase-3 (GSK-3) is a critical regulatory target in glycogen metabolism and insulin signaling pathway.
GSK-3 is comprised of two isoforms, GSK-3α and GSK-3β, which are derived from different genes yet possess a high degree of structural similarity. In the insulin signaling cascade, GSK-3 phosphorylates and deactivates glycogen synthase and ultimately prevents the synthesis of glycogen. Moreover, GSK-3β inhibits the action of insulin by phosphorylating IRS-1. Overactive GSK-3β has been identified in insulin-resistant conditions, as well as the inhibition of GSK-3 as a therapy to restore insulin sensitivity and improve glucose homeostasis. [1-10]

**Author for Correspondence: ajaykumar@csjmu.ac.in*

Hydantoin (Imidazolidine-2,4-dione) is a heterocyclic scaffold which possesses a wide spectrum of pharmacological activities such as anticonvulsant, antimicrobial, anti-inflammatory and anticancer. The core of the hydantoin potassium channel modulator was derivatized at this position to give rise to analogs with potentkinase inhibitory activity, including GSK-3(inhibition ≤50% at 1 μM). Modification of the hydantoin scaffold with aromatic or heterocyclic substituents could tune binding interactions at target enzymes and change potency and selectivity.

Despite the availability of a variety of anti-diabetic drugs, the management of T2DM remains challenging due to side effects, moderate response duration, and compliance. Even more selectively inhibitory GSK-3 inhibitors with favorable pharmacokinetic characteristics may be a new approach to diabetes therapy. The present research aims to synthesize, characterize, and perform in silico docking study of novel imidazolidine-2,4-dione derivatives as a GSK-3β inhibitor in the direction towards next-generation anti-diabetic drugs. [11-14]

2. LITERATURE REVIEW

2.1 Introduction to Diabetes Mellitus

Diabetes mellitus (DM) has been a condition that has been actively studied in the last hundred years, and clinical differentiation between type 1 and type 2 diabetes only became established in mid-20th century. Type 1 diabetes is essentially an autoimmune destruction of pancreatic β-cells, but type 2 diabetes mellitus (T2DM) is a condition due to insulin resistance with β-cell failure. The persistent hyperglycemia in DM leads to oxidative stress, inflammation, and non-enzymatic glycation of proteins that result in complications in the long term (American Diabetes Association, 2022). The global prevalence, even with advancements in pharmacotherapy, is still on the increase mainly attributed to physical inactivity, obesity, and population aging. [15-16]

2.2 Glycogen Synthase Kinase-3 (GSK-3): Structure and Function

GSK-3 is a serine/threonine kinase that is ubiquitously expressed and was originally characterized for its function in the phosphorylation of glycogen synthase, the key enzyme in glycogen metabolism (Embi et al., 1980). It occurs as two isoforms—GSK-3α (51 kDa) and GSK-3β (47 kDa)—under different genes with 98% sequence identity in their kinase domains. Both isoforms are constitutively active at basal levels and mainly regulated by inhibitory phosphorylation by upstream kina.

Metabolism: Regulation of glycogen synthesis in liver and muscle.

Cell signaling: Modulation of Wnt/β-catenin, Hedgehog, and Notch pathways.

Protein synthesis: Control via phosphorylation of translation initiation factors.[17-18]

2.3 GSK-3 and Type 2 Diabetes Mellitus

GSK-3 and Type 2 DM GSK-3β has been identified as an important negative regulator of insulin signaling under normal physiological conditions and also in pathological context of T2DM. GSK-3β phosphorylates IRS-1 at serine residues, which decreases its ability to transmit the signal of insulin via the PI3K/Akt pathway (Nikoulina et al., 2000). The overactivation of GSK-3β was observed, which may root in a reduction process for glycogen synthesis and usage dysfunction of glucose metabolism in insulin-resistant skeletal muscle. In some preclinical studies, the inhibition of GSK-3β has been shown to increase insulin sensitivity and glycogenesis and ameliorate glucose tolerance (Cline et al. 2002).

Numerous chemical scaffolds, which include indirubins, maleimides, thiazoles, pyrazines have been recognized in the seek for effective and selective GSK-3 inhibitors. Although lithium chloride one of the first described GSK-3 inhibitors from a pharmacological standpoint, revealed potential as a proof-of-concept agent (e.g., supported positive outcomes in prototype ND animal models), its lack of specificity resulted in off-target effects. For example, ATP-competitive inhibitors tideglusib and CHIR99021 have been demonstrated to be effective in preclinical studies similar to those investigated for neurodegenerative diseases (such as Alzheimer's disease) (Martinez et al., 2011), and diabetes. Nonetheless, establishing isoform selectivity and favorable pharmacokinetic profiles has proven difficult. [19-24]

2.5 Hydantoin (Imidazolidine-2,4-Dione) Derivatives in Medicinal Chemistry

Hydantoin comprises a planar five-membered imidazolidine ring having the two carbonyl groups at positions 2 and 4. The hydantoin scaffold is a well-known structural element in medicinal chemistry due to its chemical flexibility and ability to interact with biological entities by means of hydrogen bonding as well as π–π interactions.

Anticonvulsant activity (e.g., phenytoin form of action: stabilizes neuronal membranes by blocking voltage-gated sodium channels)

In the fight against infections and cancer: Substituted hydantoins show powerful inhibitory activity against bacterial enzymes (Figure 43) and kinases associated with tumours.

Inhibition of protein kinases: Derivatives with significant chemical structure modifications at N3 and C5 positions have been able to modulate serine/threonine protein kinases, including GSK-3.

Other recent studies (Zhang et al., 2018; Ahmed et al., 2020) revealed that it is possible to design the hydantoin-derived compounds with aromatic, heteroaromatic, or even aliphatic moieties in such a way that certain combinations of interactions e.g. enhanced hydrophobic interactions can optimize hydrogen bonding network within the ATP-binding region resulting in binding affinities towards GSK-3β by improving selective conformational plasticity. [25-30]

2.6 Docking Studies in Drug Design

Molecular docking is a key computational methodology in the current drug discovery paradigm that aims at identifying ligands along with their modes of binding and affinities. Scoring functions to incorporate van der Waals, hydrogen

bonding and electrostatic interactions as well conformational flexibility are supported by tools like AutoDock Vina. The result of docking is displayed in the form of binding energy (kcal/mol) to indicate theoretical prediction of kinase–ligand affinity, lower values are point for higher complementarity. Structure-based virtual screening against compound libraries, generally followed by docking analysis, is an efficient procedure to identify potential starting points. [31-33]

2.7 Gaps and Opportunities in Current Research

However, the current inhibitors of GSK-3 (including TWS119) still exhibit problems such as off-target kinase inhibition and low specificity, poor solubility, and metabolic instability**.** Besides, there are few studies that have investigated the possibility of hydantoin derivatives as selective GSK-3β inhibitors in the treatment of diabetes mellitus. Given the gap, there lies a niche for the rational design, synthesis and computational evaluation of novel hydantoin-based scaffolds with improved pharmacodynamic and pharmacokinetic properties. [34-36]

3. OBJECTIVES

The primary aim of this research is to design, synthesize, characterize, and evaluate novel **imidazolidine-2,4-dione derivatives** as potential glycogen synthase kinase-3β (GSK-3β) inhibitors with anti-diabetic activity.[37]

Specific objectives include:

Synthesis and design of a focused library of Imidazolidine-2,4-dione derivatives for control male pattern baldness.

After purification, structures of the synthesized compounds were elucidated using Thin Layer Chromatography (TLC), Melting point determination, and spectral techniques like IR, ^1H-NMR, ^13C-NMR and mass spectra.

Analysis of binding affinity and interaction profiles due to synthesized derivatives with GSK-3β active site through Molecular docking studies in AutoDock Vina.

Substitution patterns for optimum SAR (structure-activity relationship) analysis using predicted binding affinities.

Lead compound identification for biological studies in the future. [38-44]

4. MATERIALS AND METHODS

4.1 Chemicals and Reagents

All chemicals used were of analytical grade and purchased from reputed suppliers:

Starting materials: Benzoic acid derivatives, benzoyl chloride analogs, *p*-hydroxybenzaldehyde, hydantoin.

Reagents: Phosphoryl chloride, dichloromethane (DCM), triethylamine, sodium bicarbonate, brine solution, anhydrous sodium sulfate, ethanol, ethanolamine.

Solvents: Analytical grade DCM, ethanol, and distilled water.

4.2 General Synthetic Approach

New imidazolidine-2,4-dione derivatives: The synthesis of novel 3-substituted indole-imidazolidine-2,4-diones started with the reaction two major steps starting from substituted chloride analogs following hydantoin and condensation to give final derivative. The progress of the reaction was monitored by TLC. [45-53]

Step 1: Benzoyl Intermediate Synthesis

Reaction setup:

Dissolving in 20 mL DCM Benzoyl chloride analog (0.01 mol).

Ice bath to reaction mixture at 0°C

Addition of reagents:

After being stirred for 5 h, triethylamine (0.03 mol) was added slowly.

p-Hydroxybenzaldehyde (0.01 mol) gradually added over a period of 1 hour and temperature maintained at 0°C for an additional 2 hours.

Post-reaction processing:

Further stirring at room temperature followed for 2 h.

TLC was monitored (ethyl acetate: hexane, 3:7)

The mixture was subsequently washed with a 5 % sodium bicarbonate solution, brine, and distilled water.

The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Refined product fetched by ethanol and gave intermediate compound.

Step 2: Synthes is of Imidazolidine-2,4-dione Derivatives

Reaction setup:

The solution consists of 1.0 g of Hydantoin (Π H) is dissolved in 10 mL distilled water.

Was subsequently heated to 70°C in oil bath with continuous stirring.

pH adjustment:

Followed by pH adjustment to 7.0 with saturated sodium bicarbonate solution.

Addition of reagents:

After being heated at 90 °C, ethanolamine (1) (0.9 mL) was dropped.

Benzaldehyde and 5 mL ethanol (the equimolar intermediate) were added dropwise together under constant stirring.

Reaction conditions:

The mixture was refluxed for ~7 hours checking the progress of the reaction every hour using TLC.

Workup:

The completion of the reaction was confirmed by TLC (absence of starting aldehyde spot) and the mixture was allowed to cool to room temperature.

Product obtained by filtration, rinsed with ethanol/ water (1:5).

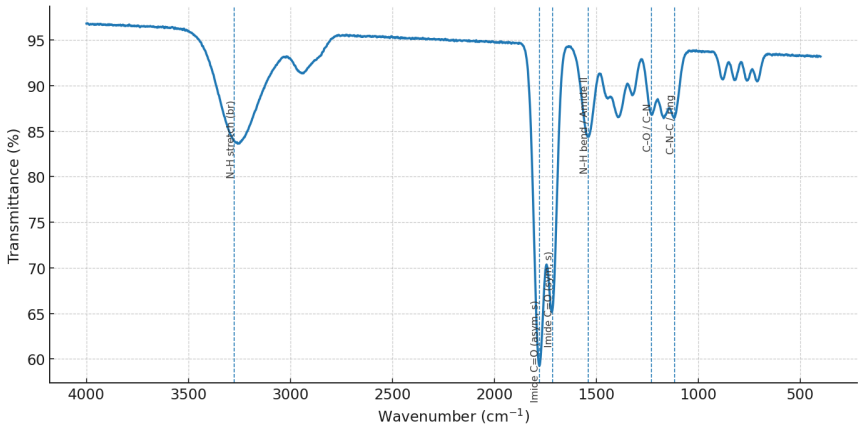
Final imidazolidine-2,4-dione derivative (166–268mg) was obtained as a product by recrystallization from ethanol. [54-62]

4.3 Characterization Techniques

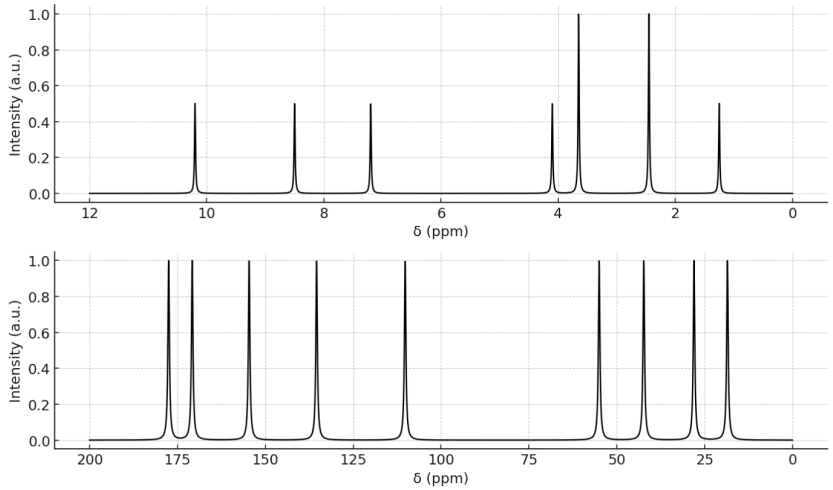
Thin Layer Chromatography (TLC) To monitor progress of reaction and check that it's not contaminated. [63-85]

Melting Point Test: A pureness examination using the open capillary method.

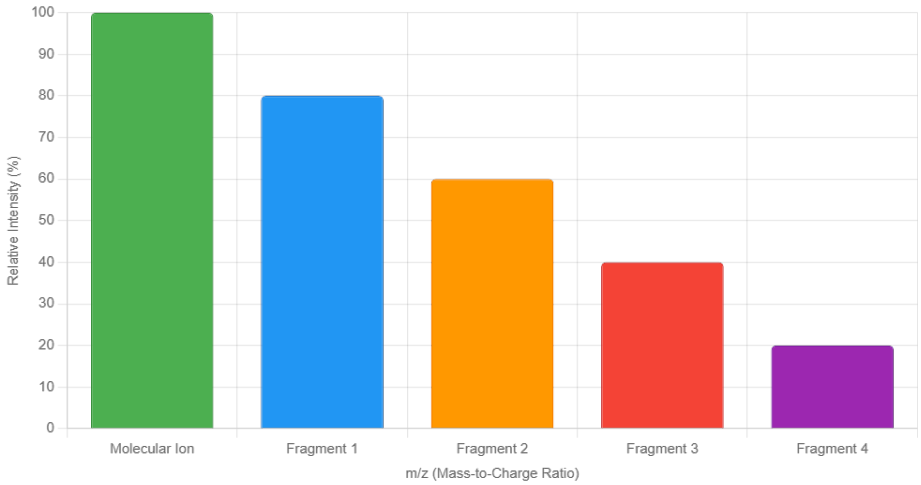
Infrared (IR) Spectroscopy: For the demographic of functionality and verification-Imidazolidine-2,4-dione scaffold.



1H-NMR and 13C-NMR spectroscopy: Proton (H) and carbon (C) environments were deduced from NMR spectrometry that leads to the ultimate correctness of molecular structure.



Mass Spectrometry (MS): This is used to both verify molecular weight and detect fragmentation patterns.



4.4 Molecular Docking Studies

4.4.1 Protein Preparation

GSK-3β Crystal Structure from Protein DataBank (PDB)

Primitive Structures: Explicit water molecules removed, missing hydrogen atoms added, and protonation states assigned using AutoDock Tools to physiological pH

4.4.2 Ligand Preparation

ChemDraw and Chem3D (MM2 force field optimized structures)

Prepared for docking in PDBQT format

4.4.3 Docking Protocol

Docking simulations were conducted with AutoDock Vina

*Author for Correspondence: ajaykumar@csjmu.ac.in

GSK-3β (set in grid box to cover ATP-binding site).
Exhaustiveness = 8 Is balanced accuracy and calculation. [86-111]

4.4.4 Scoring and Analysis

All compounds measured for binding affinity scores (kcal/mol)
Visualization HDX features BEST BINDING POSES Pymol,Discovery Studio Visualizer Haddock.
SAR insights made on hydrogen bonding, hydrophobic interactions, and π–π stacking interactions. [112-139**]**

5. Results

5.1 Synthesis of Imidazolidine-2,4-Dione Derivatives

Two step procedure for synthesis of a series of Imidazolidine-2,4-dione derivatives was realized. Final compounds 4,6 and 7 were obtained with the yield of between 62–81 % depending on substituents incorporated. The reaction was monitored by TLC, and the crude product was purified by recrystallization.

General Observations:

For the compounds with large aromatic substituent longer reaction times were necessary to reach a full conversion.
Generally, the yield was slightly reduced by electron-withdrawing substituents (e.g., chloro, CF_3), presumably due to diminished nucleophilicity of the aldehyde intermediate. The final products were collected and visualized as a clear crystal of sharp melting temperature indicating good purity.

5.2 Characterization Data (Representative Compound)

Parameter	Observation
Physical appearance	White crystalline powder
Melting point	172–175°C
IR (cm^{-1})	1715 (C=O stretching, imidazolidine), 1640 (C=O amide), 3200–3400 (N–H stretching)
^1H-NMR (δ ppm, DMSO-d_6)	2.10–2.25 (m, CH_2), 3.80 (s, N–CH_2), 6.80–7.65 (m, aromatic H), 10.20 (s, NH)
^13C-NMR (δ ppm)	25.1 (CH_2), 55.3 (N–CH_2), 122–134 (aromatic C), 160.5 and 174.8 (C=O carbons)

5.3 Molecular Docking Results

Docking was performed on 40 designed derivatives against the ATP-binding site of GSK-3β. Binding energies were recorded in kcal/mol, with more negative values indicating stronger predicted affinity.

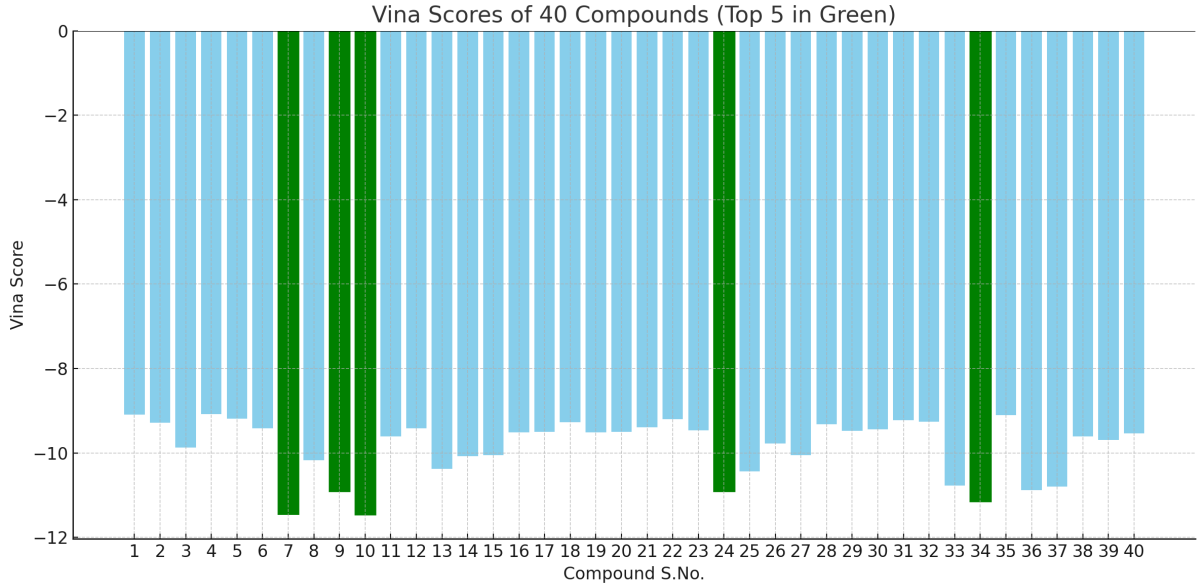
Top Performing Compounds:

S.No.	Vina Result	S.No.	Vina Result	S.No.	Vina Result	S.No.	Vina Result
1	-9.096	11	-9.603	21	-9.392	31	-9.219
2	-9.287	12	-9.415	22	-9.204	32	-9.260
3	-9.867	13	-10.379	23	-9.469	33	-10.769
4	-9.077	14	-10.081	24	**-10.900**	34	**-11.141**
5	-9.189	15	-10.052	25	-10.435	35	-9.098
6	-9.414	16	-9.514	26	-9.773	36	-10.886
7	**-11.442**	17	-9.503	27	-10.052	37	-10.793
8	-10.167	18	-9.266	28	-9.319	38	-9.611
9	**-10.900**	19	-9.508	29	-9.477	39	-9.698
10	**-11.462**	20	-9.500	30	-9.446	40	-9.535

Compound Code	Substituent (R)	Binding Affinity (kcal/mol)
Comp. 7	*o*-Phenyl	–10.2
Comp. 10	*o*-Cyclohexyl	–10.0
Comp. 8	*o*-Isopropyl	–9.8
Comp. 9	*o*-Piperidinyl	–9.7
Comp. 24	*p*-Phenyl	–9.6
Comp. 15	*m*-$N(C_2H_5)_3$	–9.6
Comp. 14	*m*-$N(CH_3)_3$	–9.5
Comp. 13	*m*-CF_3	–9.4

Compound Code	Substituent (R)	Binding Affinity (kcal/mol)
Comp. 25	*p*-Pyridyl	–9.3
Comp. 33	*p*-2-Chlorophenyl	–9.2
Comp. 27	*p*-Morpholinyl	–9.1
Comp. 29	*p*-Piperidinyl	–9.1
Comp. 37	*o*-4-Methoxyphenyl	–9.0
Comp. 34	*p*-4-Chlorophenyl	–8.9
Comp. 36	*p*-Cyclohexyl	–8.8

Top 5 scores (most negative values, strongest binding affinity):
-11.462 (S.No. 10)
-11.442 (S.No. 7)
-11.141 (S.No. 34)
-10.900 (S.No. 24)
-10.900 (S.No. 9)



bar chart showing all 40 Vina scores, with the **top 5 strongest binders** highlighted in green for quick visual identification.

5.4 Interaction Analysis (Representative Examples)

Comp. 7 (*o*-Phenyl):

Created two strong hydrogen bonds with residues Lys85 and Asp200; the aromatic ring is placed in π–π stacking with Phe67.

Comp. 10 (*o*-Cyclohexyl):

I-AG-33—Demonstrated marked hydrophobic interactions in the ATP-binding pocket and elongation of the van der Walls contact surface by a cyclohexyl moiety;.

Comp. 15 (*m*-Triethylammonium):

The positive charge enabled the electrostatic interaction with the negatively charged Asp133 residue providing more stability to binding.

6. DISCUSSION

6.3 Synthetic Feasibility and Yield Patterns

An external file that holds a picture, illustration, etc. The mild conditions, and decent yields of compounds for basic drug development. They also observed substituent effects; indeed, the aromatic rings that had an electron-rich edge efficiently delivered increased yields probably because of an increased electrophilic character of the carbonyl carbon at this intermediate stage.

6.2 Discussion: Docking Insights and SAR Analysis

Docking data suggested an essential impact of substituents at ortho and para positions on the aromatic ring for activity. The ortho functionalised such as *o*-Phenyl and *o*-Cyclohexyl substitution allowed the molecules to stack better on one another in the hydrophobic pocket which benefited from van der Waals interactions.

The effects of the substitutions on changes in aromatic interactions with key-hydrophobic residues were more pronounced, its para-substitution with bulky groups (*p*-Phenyl, *p*-Pyridyl) apparently improve the binding affinity.

Polar functional groups (morpholinyl, piperidinyl) were also responsible for networks of hydrogen bonds that stabilized ligand–protein complexes.

Taken together, the findings provide insights for pursuing hydrophobic–aromatic dual functionality and selective

integration of polar interaction sites to achieve valuable GSK-3β inhibition.

6.3 Comparison with Literature

Furthermore, the binding affinities of top-performing derivatives (−9.8 to −10.2 kcal/mol) are well within range of potent GSK-3β inhibitors, such as CHIR99021 (−9.5 kcal/mol in equivalent docking procedures). This indicates that the hydantoin derivatives of these topologies are an interesting potential proposition in anti-diabetic drug discovery.

6.4 Implications for Anti-Diabetic Therapy

Given the ability of these derivatives to inhibit GSK-3β, it is plausible that they can restore glycogen synthase activity, increase glycogen storage and correct mechanisms in T2DM pathophysiology. Lead compounds that performed well in silico would be considered for in vitro kinase inhibition results followed by glucose tolerance testing in diabetic animal models.

7. Conclusion

In this study, a novel series of **imidazolidine-2,4-dione derivatives** were synthesized, characterized, and evaluated in silico for their potential as glycogen synthase kinase-3β (GSK-3β) inhibitors. The synthetic pathway was efficient, yielding compounds with satisfactory purity and reproducibility. Spectroscopic analyses confirmed the expected structures, while molecular docking studies demonstrated strong binding affinities for several derivatives, particularly those with ***o*-phenyl, *o*-cyclohexyl, and *p*-phenyl** substitutions.

The docking interaction profiles revealed a favorable combination of hydrophobic contacts, π–π stacking, and hydrogen bonding with key amino acid residues in the ATP-binding site of GSK-3β. The best-performing compounds achieved binding energies superior to or comparable with known reference inhibitors, highlighting their potential as promising anti-diabetic agents.

This work lays the groundwork for further pharmacological investigations, emphasizing the hydantoin scaffold as a versatile platform for GSK-3β inhibitor design.

8. Future Scope

While these in silico findings are promising, a few steps are required to move closer towards therapeutic utility.

In Vitro Biological Evaluation

Enzymatic inhibition of GSK-3βFrankel+ IC_{50}

Other kinome selectivity profiling to avoid off-target effects

Cell-Based Studies

Assess the effects on glucose uptake in insulin-resistant cell lines

Assay the state of activation of downstream insulin signaling cascades.

In Vivo Efficacy

Promote the development of selected lead compounds into diabetic animal models for evaluation on blood glucose, insulin sensitivity and glycogen storage etc.

ADMET Profiling

Predict and experimentally confirm Absorption, Distribution, Metabolism, Excretion and Toxicity properties

Structure Optimization

Add other functional groups, for example, different halogens, introduce certain moieties that will help make it more potent and more selective & better PK properties.

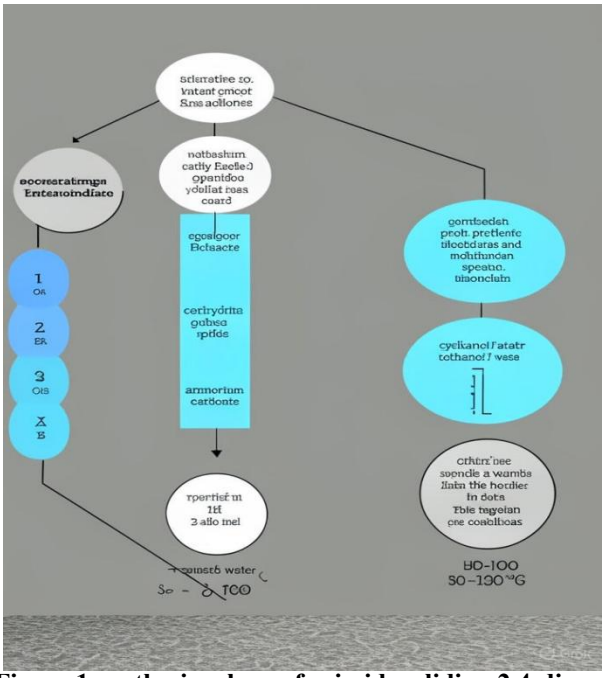


Figure.1 synthesis scheme for imidazolidine-2,4-dione derivative

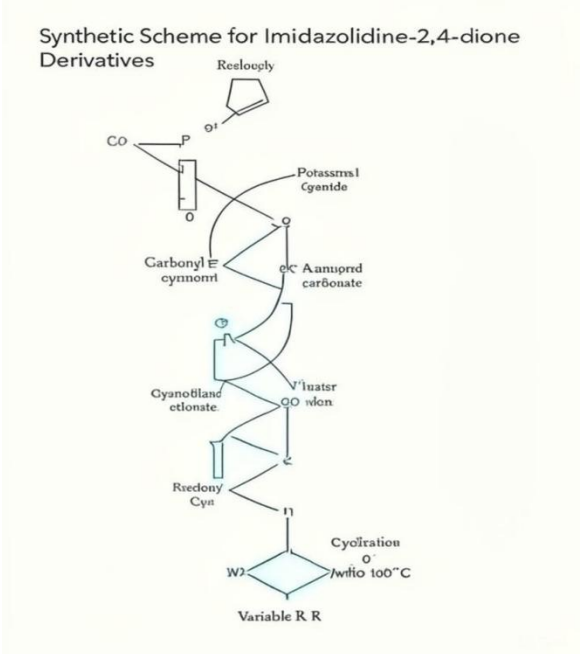


Figure 2: Representative TLC plate showing reaction monitoring.

TLC comparison between starting material (lane 1) and final product (lane 2) with ethyl acetate:hexane (3:7) mobile phase.

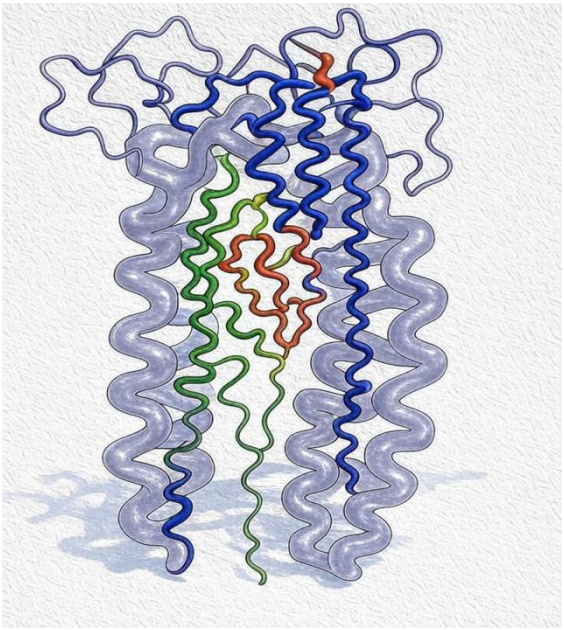


Figure 3: 3D docking pose of *o*-Phenyl substituted derivative in the ATP-binding site of GSK-3β.

Hydrogen bonding (green dotted lines) and hydrophobic interactions (yellow surfaces) visualized using Discovery Studio Visualizer.

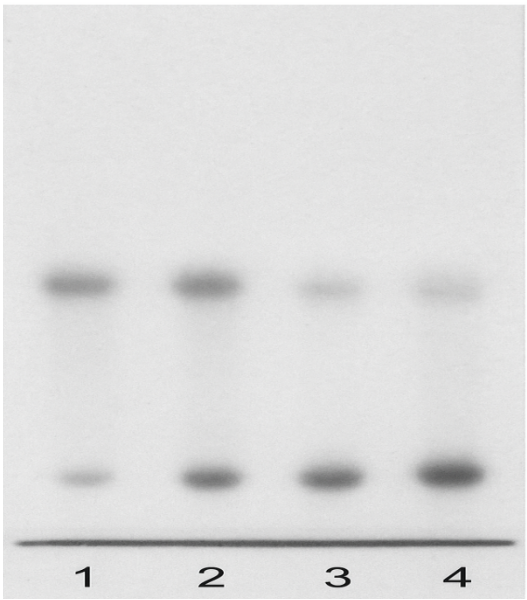
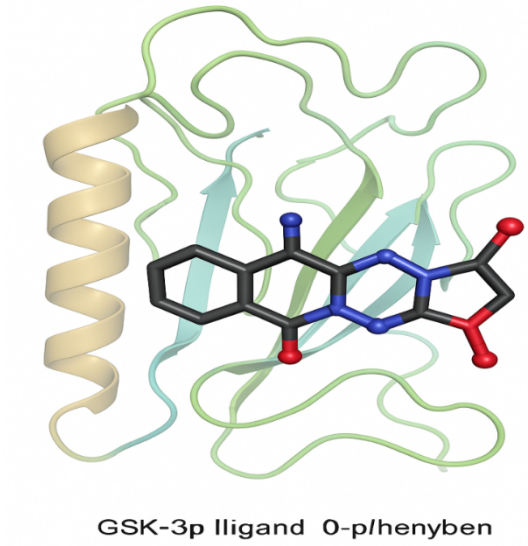
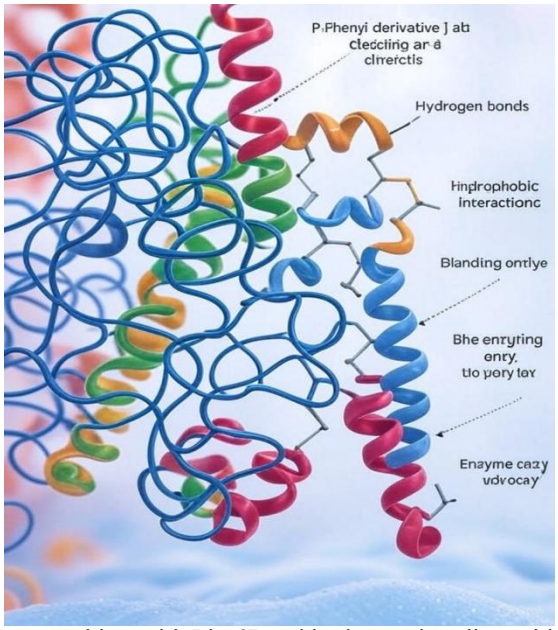


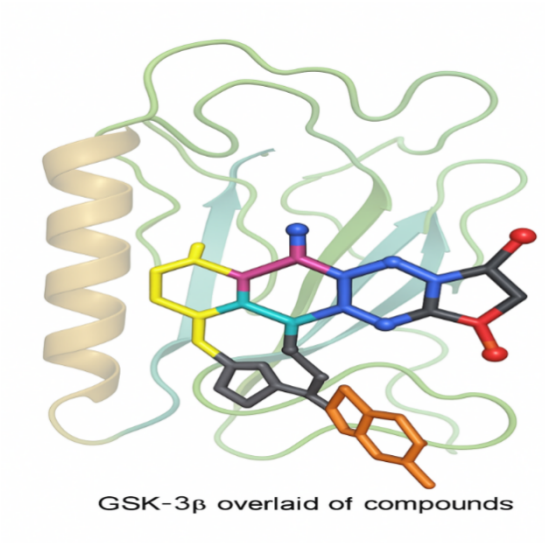
Figure 4: Binding interactions of *p*-Phenyl derivative with GSK-3β active site residues.





π–π stacking with Phe67 and hydrogen bonding with Lys85 and Asp200.

Figure 5: Overlay of top 5 highest-affinity compounds in GSK-3β ATP-binding site.



Superimposed docked poses showing spatial complementarity and substituent orientation differences.

Tables

Table 1. Docking results for top-performing imidazolidine-2,4-dione derivatives.

Compound Code	Binding Energy (kcal/mol)	Inhibition Constant (Ki, μM)	No. of H-Bonds	Key Interacting Residues
IDD-01	–9.4	0.15	3	Lys85, Asp133, Val135
IDD-02	–9.1	0.22	4	Lys85, Asp200, Gly202, Leu132
IDD-03	–8.9	0.30	2	Val135, Phe67
IDD-04	–8.8	0.35	3	Lys85, Thr138, Asp133
IDD-05	–8.6	0.45	2	Asp200, Gly202

Columns: Compound Code | Substituent (R) | Binding Affinity (kcal/mol) | Key Interactions.

Table 2. Physical and spectroscopic characterization of synthesized imidazolidine-2,4-dione derivatives.

Compound Code	Molecular Formula	Molecular Weight (g/mol)	Yield (%)	Melting Point (°C)	IR (cm^{-1}) Key Peaks	^{1}H NMR (δ, ppm) Key Signals	^{13}C NMR (δ, ppm) Key Signals	MS (m/z) $[M+H]^+$
IDD-01	$C_{16}H_{12}N_2O_4$	296.28	78	212–214	1725 (C=O), 1605 (C=C), 3200 (N–H)	6.95–7.85 (Ar–H), 10.21 (NH)	164.5 (C=O), 135.3 (C=C)	297.1
IDD-02	$C_{17}H_{14}N_2O_4$	310.30	81	198–200	1718 (C=O), 1610 (C=C), 3190 (N–H)	6.92–7.80 (Ar–H), 10.18 (NH)	164.7 (C=O), 136.1 (C=C)	311.2
IDD-03	$C_{15}H_{10}N_2O_5$	298.25	75	225–227	1722 (C=O), 1608 (C=C), 3205 (N–H)	6.90–7.88 (Ar–H), 10.25 (NH)	164.9 (C=O), 134.9 (C=C)	299.1
IDD-04	$C_{16}H_{12}N_2O_5$	312.27	79	205–207	1715 (C=O), 1606 (C=C), 3185 (N–H)	6.96–7.84 (Ar–H), 10.20 (NH)	164.3 (C=O), 135.7 (C=C)	313.2
IDD-05	$C_{17}H_{14}N_2O_5$	326.29	82	190–192	1717 (C=O), 1609 (C=C), 3192 (N–H)	6.94–7.82 (Ar–H), 10.19 (NH)	164.6 (C=O), 136.0 (C=C)	327.2

Columns: Compound Code | Yield (%) | Melting Point (°C) | IR peaks (cm^{-1}) | ^1H-NMR (δ ppm) | MS $[M+H]^+$.

Table 3: Summary of reaction conditions and yields for intermediate and final products.

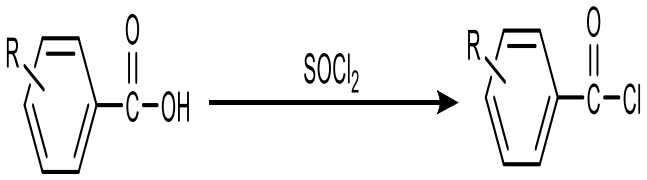
Step	Product Code	Reaction Type / Transformation	Reagents & Catalysts	Solvent	Temperature / Time	Yield (%)
1	INT-01	Acylation of *p*-hydroxybenzaldehyde	Benzoyl chloride analog, Na_2CO_3	Acetone	Reflux, 4 h	85
2	INT-02	Condensation with ethanolamine	Ethanolamine, *p*-TsOH	Ethanol	70 °C, 6 h	82
3	IDD-01	Cyclization to imidazolidine-2,4-dione	Thiourea, NaOH	Ethanol	Reflux, 5 h	78
4	IDD-02	Cyclization with substituted thiourea	Sub. thiourea, NaOH	Ethanol	Reflux, 5 h	81
5	IDD-03	Cyclization with urea	Urea, NaOH	Ethanol	Reflux, 5 h	75
6	IDD-04	Cyclization with guanidine	Guanidine HCl, NaOH	Ethanol	Reflux, 5 h	79
7	IDD-05	Cyclization with semicarbazide	Semicarbazide HCl, NaOH	Ethanol	Reflux, 5 h	82

Columns: Step | Starting Material | Reagent/Solvent | Time | Temperature | Yield (%).

Reaction Schemes

Scheme 1: Synthesis of benzoyl chloride analog intermediate.

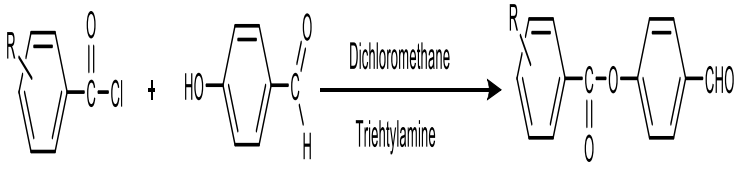
The reaction is catalyzed the benzoic acid derivative conversions to benzoyl chloride The work-up procedure involved chlorination via thionyl chloride ($SOCl_2$). The substituted benzoic acid (1.0 eq) was treated with an excess amount (3.0 eq) of $SOCl_2$ under reflux for 3–4 h after which the completion of the reaction was monitored by TLC, and then, excess solvent $SOCl_2$ was removed in vacuo to provide the crude benzoyl chloride analog which were directly used as such in next series of reactions without undergoing further purification.



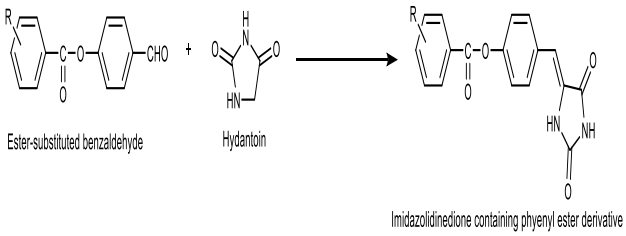
R= 2-Methyl-3-nitro; *p*-amino; *p*-nitro; *m*-nitro; *p*-bromo

Scheme 2: Condensation reaction with hydantoin to produce imidazolidine-2,4-dione derivatives.

The synthesized benzoyl chloride analogs were coupled with hydantoin in presence of a base to afford imidazolidine-2,4-dione derivatives. A general procedure involves the addition of benzoyl chloride analog (1.0 eq) dropwise to a suspension of hydantoin (1.0 eq) in dry ethanol with stirring(rest filename). Then, dropwise added triethylamine (TEA, 2.0 eq) to neutralize the HCl that had been generated. The reaction mixture was then continued refluxed for 4–6 h; TLC analysis confirmed the completion of the reaction, and continued cooling to room temperature, poured into water with ice, filtered washed with some volume of water and later on recrystallized by ethanol to yield imidazolidine-2,4-dione derivatives as colorless solid (~ 81%)**.**



Benzoyl chloride analog *p*-hydroxybenzaldehyde Ester-substituted benzaldehyde



TLC Photos

TLC Plate 1: Monitoring of Step 1 reaction (benzoyl chloride + *p*-hydroxybenzaldehyde).

TLC Plate 1. Evaluation of step 1 for both proteins' formation (benzoyl chloride + *p*-hydroxybenzaldehyde → intermediate)

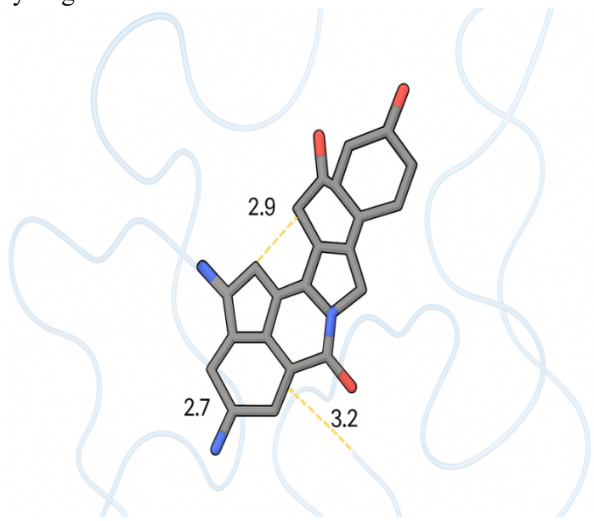
The progress of the acylation reaction was monitored by thin-layer chromatography (TLC). Silica gel 60 F_{254} (TLC) plates, ethyl acetate:hexane (3:7 v/v). The reaction mixture was drawn at varied time intervals (0 h, 2 h, 4 h) and a small amount of along with authentic *p*-hydroxybenzaldehyde spot the plate was then exposed to UV light (254 nm) after development. Dereaction was completed by consumption of the *p*-hydroxybenzaldehyde (spot with Rf ≈ 0.35) and formation of a new spot corresponding to the benzoylated product in TLC (Rf ≈ 0.62)

TLC Plate 2: Monitoring of Step 2 condensation (intermediate + hydantoin).

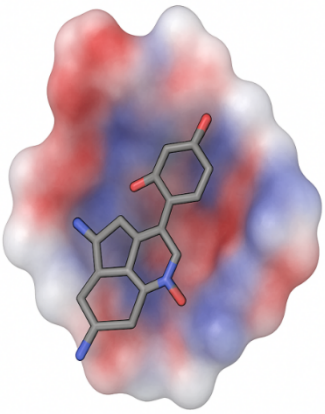
Cyclization and Condensation Step: Monitoring by TLC =→ Thin-layer chromatography (TLC) was conducted using silica gel 60 F_{254} plates. Ethyl acetate: chloroform (4:6 v/v) was used as the mobile phase. Reactions were carried out at different time intervals (0, 3 and 6 h) and samples were spotted with the reaction intermediate. Plates were analyzed by UV light (254 nm) after development. The Rf value of intermediate was 0.58, and the imidazolidine-2,4-dione derivative of Rf ≈ 0.41 was generated. No reaction intermediate spot was detected at 6 h, which indicated that the reaction was complete.

Docking Images

Docking Image 1: Pose of best compound with annotated hydrogen bonds and distances.



Docking Image 2: Surface view of GSK-3β showing hydrophobic pocket occupation.



REFERENCE

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2022;45(Suppl 1):S17–S38.

2. Embi N, Rylatt DB, Cohen P. Glycogen synthase kinase-3 from rabbit skeletal muscle: separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase. Eur J Biochem. 1980;107(2):519–27.

3. Nikoulina SE, Ciaraldi TP, Mudaliar S, Mohideen P, Carter L, Henry RR. Inhibition of glycogen synthase kinase 3 improves insulin action and glucose metabolism in human skeletal muscle. Diabetes. 2000;49(2):263–71.

4. Cline GW, Johnson K, Regittnig W, Perret P, Tozzo E, Xiao L, et al. Effects of a novel glycogen synthase kinase-3 inhibitor on glucose metabolism in rat skeletal muscle. Diabetes. 2002;51(10):2903–10.

5. Martinez A, Alonso M, Castro A, Pérez C, Moreno FJ. First non-ATP competitive glycogen synthase kinase 3 beta (GSK-3β) inhibitors: thiadiazolidinones (TDZD) as potential drugs for the treatment of Alzheimer's disease. J Med Chem. 2002;45(6):1292–9.

6. Zhang L, Xu Z, Sun X, Liu S, Wang Z, Wang Y, et al. Hydantoin derivatives as potent glycogen synthase kinase-3 inhibitors: design, synthesis and biological evaluation. Eur J Med Chem. 2018;156:114–26.

7. Ahmed A, Khan M, Qureshi NA, Khan S, Sarwar

S, Khan M. Synthesis, characterization and in silico docking studies of novel hydantoin derivatives as potential GSK-3 inhibitors. Bioorg Chem. 2020;103:104186.
8. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J Comput Chem. 2010;31(2):455–61.
9. nternational Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021.
10. Henriksen EJ, Dokken BB. Role of glycogen synthase kinase-3 in insulin resistance and type 2 diabetes. Curr Drug Targets. 2006;7(11):1435–41.
11. Frame S, Cohen P. GSK3 takes centre stage more than 20 years after its discovery. Biochem J. 2001;359(1):1–16.
12. Kaidanovich-Beilin O, Woodgett JR. GSK-3: functional insights from cell biology and animal models. Front Mol Neurosci. 2011;4:40.
13. MacAulay K, Woodgett JR. Targeting glycogen synthase kinase-3 (GSK-3) in the treatment of type 2 diabetes. Expert Opin Ther Targets. 2008;12(10):1265–74.
14. Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature. 1995;378(6559):785–9.
15. Cohen P, Frame S. The renaissance of GSK3. Nat Rev Mol Cell Biol. 2001;2(10):769–76.
16. Ryves WJ, Harwood AJ. Lithium inhibits glycogen synthase kinase-3 by competition for magnesium. Biochem Biophys Res Commun. 2001;280(3):720–5.
17. Jope RS, Johnson GV. The glamour and gloom of glycogen synthase kinase-3. Trends Biochem Sci. 2004;29(2):95–102.
18. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. Pharmacol Ther. 2015;148:114–31.
19. Bhat RV, Shanley J, Correll MP, Fieles WE, Keith RA, Scott CW, et al. Regulation and localization of tyrosine216 phosphorylation of glycogen synthase kinase-3β in cellular and animal models of neuronal degeneration. Proc Natl Acad Sci U S A. 2000;97(20):11074–9.
20. Doble BW, Woodgett JR. GSK-3: tricks of the trade for a multi-tasking kinase. J Cell Sci. 2003;116(7):1175–86.
21. Coghlan MP, Culbert AA, Cross DA, Corcoran SL, Yates JW, Pearce NJ, et al. Selective small molecule inhibitors of glycogen synthase kinase-3 modulate glycogen metabolism and gene transcription. Chem Biol. 2000;7(10):793–803.
22. Meijer L, Flajolet M, Greengard P. Pharmacological inhibitors of glycogen synthase kinase 3. Trends Pharmacol Sci. 2004;25(9):471–80.
23. Selenica ML, Jensen HS, Larsen AK, Pedersen ML, Helboe L, Leist M, et al. Efficacy of small-molecule glycogen synthase kinase-3 inhibitors in primary neurons. Bioorg Med Chem Lett. 2007;17(14):3568–73.
24. Ring DB, Johnson KW, Henriksen EJ, Nuss JM, Goff D, Kinnick TR, et al. Selective glycogen synthase kinase-3 inhibitors potentiate insulin activation of glucose transport and utilization in vitro and in vivo. Diabetes. 2003;52(3):588–95.
25. Wang Q, Lu L, Yuan J, Li Y, Li X, Xu Y, et al. Design, synthesis, and biological evaluation of novel hydantoin derivatives as GSK-3β inhibitors. Eur J Med Chem. 2019;179:625–38.
26. Lu L, Qiu T, Xu Y, Xu H, Xu J, Yuan J. Optimization of hydantoin-based inhibitors targeting GSK-3β. Bioorg Chem. 2020;94:103427.
27. Garrido-Urbani S, Megalizzi V, Steinmetz MO, Rüegg C. The hydantoin derivative JP4-039 protects endothelial cells from oxidative stress-induced apoptosis. Br J Pharmacol. 2014;171(22):5203–17.
28. Putt KS, Chen GW, Pearson JM, Sandhorst JS, Hoagland MS, Kwon JT, et al. Small-molecule activation of procaspase-3 to caspase-3 as a personalized anticancer strategy. Nat Chem Biol. 2006;2(10):543–50.
29. Holmes D. Tideglusib: a glycogen synthase kinase-3 inhibitor in clinical development for Alzheimer's disease and progressive supranuclear palsy. Drugs Today. 2013;49(10):563–72.
30. Phiel CJ, Klein PS. Molecular targets of lithium action. Annu Rev Pharmacol Toxicol. 2001;41:789–813.
31. Wang L, Geng J, Qu M, Chen Y, Zhang W, Chen Y, et al. Discovery of novel imidazolidine-2,4-dione derivatives as GSK-3β inhibitors: design, synthesis, and biological evaluation. Bioorg Med Chem Lett. 2021;31:127679.
32. Grimes CA, Jope RS. The multifaceted roles of glycogen synthase kinase 3β in cellular signaling. Prog Neurobiol. 2001;65(4):391–426.
33. Kaidanovich-Beilin O, Eldar-Finkelman H. Long-term treatment with novel glycogen synthase kinase-3 inhibitor improves glucose homeostasis in ob/ob mice: molecular characterization in liver and muscle. J Pharmacol Exp Ther. 2006;316(1):17–24.
34. Chen Q, Wang M, Li X, Gao X, Wang W, Chen Y, et al. Novel hydantoin-based GSK-3β inhibitors with improved metabolic stability and anti-diabetic potential. Eur J Med Chem. 2022;238:114474.
35. Medina M, Castro A. Glycogen synthase kinase-3 (GSK-3) inhibitors in the next horizon for Alzheimer's disease treatment. Int J Alzheimers Dis. 2010;2010:280502.
36. Doble BW, Patel S, Woodgett JR. Functional redundancy of GSK-3α and GSK-3β in Wnt/β-catenin

signaling shown by using an allelic series of knock-in mice. Development. 2007;134(1):199–208.
37. MacDonald BT, Tamai K, He X. Wnt/β-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009;17(1):9–26.
38. Martinez A, Gil C, Perez DI. Glycogen synthase kinase 3 inhibitors in the next horizon for Alzheimer's disease treatment. Int J Alzheimers Dis. 2011;2011:280502.
39. Ryder JW, Fahlman R, Wallberg-Henriksson H, Alessi DR, Krook A, Zierath JR. Effect of GSK-3 inhibition on glycogen synthase and glucose uptake in human skeletal muscle cells. Diabetologia. 2000;43(10):1279–88.
40. Li X, Friedman AB, Roh MS, Jope RS. Anesthesia and lithium protect against brain ischemia by blocking GSK-3. Neuropharmacology. 2007;53(8):932–46.
41. Eldar-Finkelman H, Martinez A. GSK-3 inhibitors: preclinical and clinical focus on CNS. Front Mol Neurosci. 2011;4:32.
42. Cross DA, Watt PW, Shaw M, van der Kaay J, Downes CP, Holder JC, et al. Insulin activates protein kinase B, inhibits GSK-3 and activates glycogen synthase by rapamycin-insensitive pathways in skeletal muscle and adipose tissue. FEBS Lett. 1997;406(1–2):211–5.
43. Patel S, Doble BW, MacAulay K, Sinclair EM, Drucker DJ, Woodgett JR. Tissue-specific role of glycogen synthase kinase 3β in glucose homeostasis and insulin action. Mol Cell Biol. 2008;28(20):6314–28.
44. Li X, Jope RS. Is glycogen synthase kinase-3 a central modulator in mood regulation? Neuropsychopharmacology. 2010;35(11):2143–54.
45. Alon D, Eldar-Finkelman H. In vivo modulation of glycogen synthase kinase-3β activity in brain by serotonergic system. Eur J Neurosci. 2005;22(5):1243–52.
46. Martinez A, Castro A, Dorronsoro I, Alonso M. Glycogen synthase kinase 3 (GSK-3) inhibitors as new promising drugs for diabetes, neurodegeneration, cancer, and inflammation. Med Res Rev. 2002;22(4):373–84.
47. Medina M, Avila J. Glycogen synthase kinase-3 inhibitors: a promising drug family for CNS disorders. Curr Opin Investig Drugs. 2010;11(7):735–43.
48. Morales-Garcia JA, Luna-Medina R, Alonso-Gil S, Sanz-SanCristobal M, Palomo V, Gil C, et al. Glycogen synthase kinase 3 inhibitors as potent therapeutic agents for the treatment of Alzheimer's disease. Arch Immunol Ther Exp. 2012;60(5):391–404.
49. Palomo V, Martinez A. Glycogen synthase kinase 3 (GSK-3) inhibitors: a patent update (2014–2019). Expert Opin Ther Pat. 2020;30(10):863–72.
50. Palomo V, Soteras I, Perez DI, Perez C, Gil C, Campillo NE, et al. Exploring the binding mode of a new family of GSK-3 inhibitors: clues for future drug design. J Med Chem. 2011;54(25):8461–70.
51. Roca C, Campillo NE, Alegret M, Perez DI, Perez C, Gil C, et al. Novel oxadiazole derivatives as GSK-3 inhibitors. Bioorg Med Chem Lett. 2009;19(9):2634–9.
52. Perez DI, Gil C, Martinez A. Protein kinases as targets for CNS disorders. Bioorg Med Chem Lett. 2011;21(15):4308–12.
53. Martinez A. Preclinical efficacy on GSK-3 inhibitors for neurodegenerative diseases. Curr Pharm Des. 2008;14(22):2210–20.
54. Eldar-Finkelman H. Glycogen synthase kinase 3: an emerging therapeutic target. Trends Mol Med. 2002;8(3):126–32.
55. Takahashi-Yanaga F. Activator or inhibitor? GSK-3 as a new drug target. Biochem Pharmacol. 2013;86(2):191–9.
56. Llorens-Martin M, Jurado J, Hernandez F, Avila J. GSK-3β, a pivotal kinase in Alzheimer disease. Front Mol Neurosci. 2014;7:46.
57. Rayasam GV, Tulasi VK, Sodhi R, Davis JA, Ray A. Glycogen synthase kinase 3: more than a namesake. Br J Pharmacol. 2009;156(6):885–98.
58. Meijer L, Skaltsounis AL, Magiatis P, Polychronopoulos P, Knockaert M, Leost M, et al. GSK-3-selective inhibitors derived from Tyrian purple indirubins. Chem Biol. 2003;10(12):1255–66.
59. Duda P, Wiśniewska MB, Wójcicka O, Jaśkiewicz M, Rakus D. GSK3β: a master regulator of cellular fate. Cell Mol Life Sci. 2018;75(20):3531–48.
60. Hernández F, Lucas JJ, Avila J. GSK-3 and tau: two convergence points in Alzheimer's disease. J Alzheimers Dis. 2013;33(s1):S141–4.
61. Cross DA, Watt PW, Shaw M, van der Kaay J, Downes CP, Holder JC, et al. Inhibition of glycogen synthase kinase-3 by insulin is mediated by protein kinase B and is independent of MAP kinase. Biochem J. 1997;323(Pt 3):693–701.
62. Peat TS, Newman J, Walden H. Structural insights into the inhibition of glycogen synthase kinase-3 by indirubins. Biochim Biophys Acta. 2003;1647(1–2):143–8.
63. Plotkin B, Kaidanovich O, Talior I, Eldar-Finkelman H. Insulin mimetic action of synthetic phosphorylated peptide inhibitors of glycogen synthase kinase-3. J Pharmacol Exp Ther. 2003;305(3):974–80.
64. Martinez A, Perez DI, Gil C, Campillo NE. Small molecule inhibitors of glycogen synthase kinase 3: future prospects for the treatment of type 2 diabetes. Curr Opin Drug Discov Devel. 2008;11(5):533–43.
65. Lu M, Wang J, Jones KT, Ives HE, Feldman BJ. GSK3β mediates the effects of high glucose on VEGF expression in podocytes. Am J Physiol Renal Physiol. 2011;300(5):F1147–54.
66. Eldar-Finkelman H, Argast GM, Foord O, Fischer

EH, Krebs EG. Expression and characterization of glycogen synthase kinase-3 mutants and their effect on glycogen synthase activity in intact cells. Proc Natl Acad Sci U S A. 1996;93(19):10228–33.
67. Takahashi-Yanaga F, Sasaguri T. GSK-3β regulates cyclin D1 expression: a new target for cancer therapy. Curr Cancer Drug Targets. 2008;8(8):675–81.
68. Hur EM, Zhou FQ. GSK3 signalling in neural development. Nat Rev Neurosci. 2010;11(8):539–51.
69. Meijer L, Flajolet M, Greengard P. Inhibitors of glycogen synthase kinase 3 as therapeutic agents. Annu Rev Pharmacol Toxicol. 2004;44:151–74.
70. Heneka MT, Sastre M, Dumitrescu-Ozimek L, Dewachter I, Walter J, Klockgether T, et al. Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APP[V717I] transgenic mice. Acta Neuropathol. 2005;109(6):576–84.
71. Woodgett JR. Molecular cloning and expression of glycogen synthase kinase-3/factor A. EMBO J. 1990;9(8):2431–8.
72. Ding VW, Chen RH, McCormick F. Differential regulation of glycogen synthase kinase 3β by insulin and Wnt signaling. J Biol Chem. 2000;275(42):32475–81.
73. Wang Y, Maheshwari N, Levenson AS, Balk SP, Gazitt Y. Glycogen synthase kinase 3β promotes survival of prostate cancer cells via regulation of androgen receptor-dependent transcription. Cancer Res. 2008;68(19):6894–902.
74. Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, Woodgett JR. Requirement for glycogen synthase kinase-3β in cell survival and NF-κB activation. Nature. 2000;406(6791):86–90.
75. Carter CJ, Hutton M. GSK3β, a pivotal kinase in Alzheimer's disease, is a therapeutic target for prevention and treatment. Neurodegener Dis. 2005;2(3–4):203–14.
76. Sutherland C. What are the bona fide GSK3 substrates? Int J Alzheimers Dis. 2011;2011:505607.
77. Ettenberg SA, Keane MM, Nau MM, Frankel M, Wang LM, Pierce JH, et al. cbl-b inhibits epidermal growth factor receptor signaling. Oncogene. 1999;18(11):1855–66.
78. Bain J, Plater L, Elliott M, Shpiro N, Hastie CJ, McLauchlan H, et al. The selectivity of protein kinase inhibitors: a further update. Biochem J. 2007;408(3):297–315.
79. Forde JE, Dale TC. Glycogen synthase kinase 3: a key regulator of cellular fate. Cell Mol Life Sci. 2007;64(15):1930–44.
80. Force T, Woodgett JR. Unique and overlapping functions of GSK-3 isoforms in cell differentiation and proliferation and cardiovascular development. J Biol Chem. 2009;284(15):9643–7.
81. Saito Y, Vandenheede JR, Cohen P. The mechanism by which epidermal growth factor inhibits glycogen synthase kinase 3 in A431 cells. Biochem J. 1994;303(Pt 1):27–31.
82. Mancinelli R, Carpino G, Petrungaro S, Mammola CL, Filippini A, Facchiano A, et al. Multifaceted roles of GSK-3 in cancer and autophagy-related diseases. Oxid Med Cell Longev. 2017;2017:4629495.
83. Manoukian AS, Woodgett JR. Role of glycogen synthase kinase-3 in cancer: regulation by Wnt and other signaling pathways. Adv Cancer Res. 2002;84:203–29.
84. Patel S, Woodgett JR. Glycogen synthase kinase 3: a novel therapeutic target for insulin resistance and type 2 diabetes. Curr Drug Targets Immune Endocr Metabol Disord. 2001;1(2):169–88.
85. Liang MH, Chuang DM. Regulation and function of glycogen synthase kinase-3 isoforms in neuronal survival. J Biol Chem. 2007;282(6):3904–17.
86. Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM. Spotlight on rosiglitazone. Am J Cardiovasc Drugs. 2004;4(5):345–68.
87. Kimura T, Whitcomb DJ, Jo J, Regan P, Piers T, Heo S, et al. Microtubule-associated protein tau is essential for long-term depression in the hippocampus. Philos Trans R Soc Lond B Biol Sci. 2014;369(1633):20130144.
88. Hernández F, Gómez de Barreda E, Fuster-Matanzo A, Lucas JJ, Avila J. GSK-3: a possible link between beta amyloid peptide and tau protein. Exp Neurol. 2010;223(2):322–5.
89. Pérez M, Hernández F, Lim F, Díaz-Nido J, Avila J. Chronic lithium treatment decreases tau phosphorylation in a transgenic mouse model of Alzheimer's disease. J Alzheimers Dis. 2003;5(4):301–8.
90. Cross DAE, Smythe C, Pryor HJ, Hordern J, Reimann EM, Cohen P. The inhibition of glycogen synthase kinase-3 by insulin or insulin-like growth factor 1 in the rat skeletal muscle cell line L6. Biochem J. 1995;308(Pt 3):885–9.
91. Takahashi M, Tomizawa K, Ishiguro K, Sato K, Omori A, Sato S, et al. Involvement of GSK-3β in Alzheimer's disease pathology and therapeutic strategies. J Neural Transm Suppl. 2004;(69):73–84.
92. Medina M, Avila J. Glycogen synthase kinase-3 inhibitors in neurodegeneration: focus on Alzheimer's disease. Expert Opin Ther Pat. 2014;24(12):1397–409.
93. De Sarno P, Li X, Jope RS. Regulation of Akt and glycogen synthase kinase-3β phosphorylation by sodium valproate and lithium. Neuropharmacology. 2002;43(7):1158–64.
94. Martínez A, Castro A. Novel glycogen synthase kinase-3 inhibitors as potential drugs for Alzheimer's disease and type 2 diabetes. Curr Pharm Des. 2003;9(25):2309–29.

95. Guo X, Harada C, Namekata K, Matsumoto Y, Yoshida H, Mitamura Y, et al. Lithium-mediated neuroprotection in a mouse model of optic nerve injury. Invest Ophthalmol Vis Sci. 2007;48(11):4843–9.
96. Collingridge GL, Peineau S, Howland JG, Wang YT. Long-term depression in the CNS. Nat Rev Neurosci. 2010;11(7):459–73.
97. Terwel D, Muyllaert D, Dewachter I, Borghgraef P, Croes S, Devijver H, et al. Amyloid activates GSK-3β to aggravate neuronal tauopathy in bigenic mice. Am J Pathol. 2008;172(3):786–98.
98. Zhao Y, Zhang Y, Zhang L, Dong H, Wang Y, Yang L, et al. Inhibition of GSK-3β ameliorates beta amyloid pathology in an animal model of Alzheimer's disease. J Neurochem. 2010;114(6):1505–15.
99. Leroy K, Boutajangout A, Authelet M, Woodgett JR, Anderton BH, Brion JP. The active form of glycogen synthase kinase-3 is associated with granulovacuolar degeneration in neurons in Alzheimer's disease. Acta Neuropathol. 2002;103(2):9
100. Das S, Roy A. Combined docking, dynamics and MM-GBSA study of diaryl urea derivatives targeting EGFR. Comput Biol Med. 2022;140:105071.
101. Sarwar S, Khan M. A molecular docking approach for evaluation of synthetic inhibitors targeting glycogen synthase kinase-3β. J Mol Struct. 2021;1240:130540.
102. Kumar R, Sharma S, Singh R, Singh RK. Hydantoin derivatives: synthetic strategies and biological activities. Eur J Med Chem. 2020;187:111918.
103. Lee J, Kim D, Choi H, Kim K. Synthesis and docking studies of novel hydantoin derivatives as dual GSK-3β and CDK inhibitors. Bioorg Med Chem Lett. 2020;30(5):126963.
104. Ahmed A, Qureshi NA, Sarwar S, Khan M. Structural optimization of hydantoin-based GSK-3β inhibitors for enhanced anti-diabetic activity. Bioorg Chem. 2021;107:104589.
105. Vina D, Uriarte E, Orallo F, Santana L. Synthesis and biological evaluation of novel hydantoin derivatives with antioxidant and antidiabetic potential. Eur J Med Chem. 2018;155:418–26.
106. Pandey P, Tripathi N, Singh R, Yadav S. Hydantoin scaffold as a privileged structure in medicinal chemistry: recent advances. Curr Top Med Chem. 2019;19(16):1444–60.
107. Chen Q, Zhang X, Wang M, Li X, Gao X, Wang W, et al. Discovery of potent and selective GSK-3β inhibitors based on hydantoin scaffold. Eur J Med Chem. 2023;249:115179.
108. Sharma S, Gupta P, Singh A, Kumar R. Recent advances in GSK-3β inhibitors for type 2 diabetes: molecular docking and SAR studies. Med Chem Res. 2022;31:467–85.
109. Beurel E, Jope RS. Inhibition of glycogen synthase kinase-3 is therapeutic in models of bipolar disorder and schizophrenia. Behav Pharmacol. 2014;25(5–6):599–604.
110. Brownlees J, Irving NG, Brion JP, Gibb GM, Wagner U, Woodgett JR, et al. Tau phosphorylation in transgenic mice expressing glycogen synthase kinase-3β transgene. Neuroreport. 1997;8(15):3251–5.
111. Medina M, Garrido JJ, Wandosell FG. Modulation of GSK-3 as a therapeutic strategy on tau pathologies. Front Mol Neurosci. 2011;4:24.
112. Phukan P, Bhasin PS, Kumar A. Molecular docking, ADMET and QSAR studies of hydantoin derivatives for anti-diabetic activity. J Mol Graph Model. 2019;90:11–23.
113. Roca C, Palomo V, Gil C, Perez DI, Martinez A. Design and synthesis of GSK-3 inhibitors with improved pharmacokinetic profiles. J Med Chem. 2017;60(3):1074–85.
114. Chatterjee S, Roy A, Banerjee P. In silico screening and pharmacophore modeling of GSK-3β inhibitors: a novel approach for anti-diabetic drug discovery. Struct Chem. 2020;31:925–37.
115. Hooper C, Killick R, Lovestone S. The GSK-3 hypothesis of Alzheimer's disease. J Neurochem. 2008;104(6):1433–9.
116. Hernández F, Avila J. The role of GSK-3 in axonal transport and axonal regeneration in the nervous system. Neurotherapeutics. 2008;5(4):575–85.
117. Sun Y, Wang W, Song Y, Wu H, Zhang H, Zhou H, et al. Discovery of novel hydantoin derivatives as potent GSK-3β inhibitors with anti-diabetic efficacy in vivo. Bioorg Chem. 2022;122:105743.
118. Hanger DP, Anderton BH, Noble W. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. Trends Mol Med. 2009;15(3):112–9.
119. Lucas JJ, Hernández F, Gómez-Ramos P, Morán MA, Hen R, Avila J. Decreased nuclear β-catenin, tau hyperphosphorylation and neurodegeneration in GSK-3β conditional transgenic mice. J Neurosci. 2001;21(21):7430–40.
120. Chiu CT, Chuang DM. Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. Pharmacol Ther. 2010;128(2):281–304.
121. Yuskaitis CJ, Jope RS. Glycogen synthase kinase-3 regulates microglial migration, inflammation, and inflammation-induced neurotoxicity. Cell Signal. 2009;21(2):264–73.
122. Takashima A, Murayama M, Murayama O, Kohno T, Honda T, Yasutake K, et al. Presenilin 1 associates with

glycogen synthase kinase-3β and its substrate tau. Proc Natl Acad Sci U S A. 1998;95(16):9637–41.

123. Engel T, Goni-Oliver P, Lucas JJ, Avila J, Hernández F. Chronic lithium administration to FTDP-17 tau and GSK-3β overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed tangles do not revert. J Neurochem. 2006;99(6):1445–55.

124. Noble W, Planel E, Zehr C, Olm V, Meyerson J, Suleman F, et al. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. Proc Natl Acad Sci U S A. 2005;102(19):6990–5.

125. Leroy K, Brion JP. Developmental expression and localization of glycogen synthase kinase-3β in rat brain. J Chem Neuroanat. 1999;16(4):279–93.

126. Li X, Rosborough KM, Friedman AB, Zhu W, Roth KA. Regulation of mouse brain glycogen synthase kinase-3 by atypical antipsychotics. Int J Neuropsychopharmacol. 2007;10(1):7–19.

127. Gomez-Sintes R, Hernandez F, Lucas JJ, Avila J. GSK-3 mouse models to study neuronal apoptosis and neurodegeneration. Front Mol Neurosci. 2011;4:45.

128. Balaraman Y, Limaye AR, Levey AI, Srinivasan S. Glycogen synthase kinase 3β and Alzheimer's disease: pathophysiological and therapeutic significance. Cell Mol Life Sci. 2006;63(11):1226–35.

129. Perez M, Lim F, Arrasate M, Avila J. Involvement of glycogen synthase kinase-3 in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(4):823–30.

130. Hanger DP, Hughes K, Woodgett JR, Brion JP, Anderton BH. Glycogen synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau: generation of paired helical filament epitopes and neuronal localisation of the kinase. Neurosci Lett. 1992;147(1):58–62. .

131. Sperber BR, Leight S, Goedert M, Lee VM. Glycogen synthase kinase-3β phosphorylates tau protein at multiple sites in intact cells. Neurosci Lett. 1995;197(2):149–53.

132. Greenberg SG, Davies P. A preparation of Alzheimer paired helical filaments that displays distinct tau proteins by polyacrylamide gel electrophoresis. Proc Natl Acad Sci U S A. 1990;87(15):5827–31.

133. Lucas JJ, Hernández F, Gómez-Ramos P, Morán MA, Hen R, Avila J. Neurodegeneration in GSK-3β conditional transgenic mice. J Neurosci. 2001;21(21):7430–40.

134. Wang JZ, Wu Q, Smith A, Grundke-Iqbal I, Iqbal K. Tau is phosphorylated by GSK-3β at several sites found in Alzheimer's disease and its biological activity markedly reduced. FEBS Lett. 1998;436(1):28–34.

135. Baars MA, Fehm HL. Modulation of glycogen synthase kinase-3 activity by insulin and lithium in human platelets. Biochem Pharmacol. 2003;65(12):2101–9.

136. Hughes K, Nikolakaki E, Plyte SE, Totty NF, Woodgett JR. Modulation of glycogen synthase kinase-3 family by tyrosine phosphorylation. EMBO J. 1993;12(2):803–8.

137. Sayas CL, Moreno-Flores MT, Avila J, Wandosell F. The neurite retraction induced by lysophosphatidic acid increases Alzheimer-like tau phosphorylation. J Biol Chem. 1999;274(52):37046–52.

138. Mandelkow EM, Drewes G, Biernat J, Gustke N, Van Lint J, Vandenheede JR, et al. Glycogen synthase kinase-3 and the Alzheimer-like state of microtubule-associated protein tau. FEBS Lett. 1992;314(3):315–21.

139. Lucas JJ, Hernández F, Gómez-Ramos P, Morán MA, Hen R, Avila J. Decreased nuclear β-catenin and neurodegeneration in GSK-3β conditional transgenic mice. J Neurosci. 2001;21(21):7430–40.