2. LITERATURE SURVEY

1. Arfeen M et al \(^1\) reported that Glycogen Synthase Kinase-3 (GSK-3) is a constitutively acting multifunctional serine/threonine kinase, a role of which has been marked in several physiological pathways, making it a potential target for the treatment of many diseases, including Type-II diabetes and Alzheimer's. Design of GSK-3β selective inhibitor was the key challenge which led to the use of rational approaches like structure based methods (molecular docking), and ligand based methods (QSAR, pharmacophore mapping) studies. These methods provide insights into the enzyme-ligand interactions and structure activity relationship of different sets of compounds for the design of promising GSK-3 inhibitors. Molecular dynamic simulation studies have additionally been performed to address key issues like the unique requirement of prime phosphorylation of its substrate at P+4 by GSK-3β. An allosteric site has also been reported, where the binding of the peptide leads to the stabilization of the activation loop, resulting in the enhancement of the catalysis of enzymes. These studies are becoming useful in the design of therapeutically active discriminatory GSK-3 inhibitors. In this article, we present a review of recent efforts and future opportunities for the design of selective GSK-3β inhibitors.

2. Henriksen EJ reported that Insulin resistance of glucose transport and metabolism in insulin-sensitive tissues is a primary defect leading to the development of type 2 diabetes. While the etiology of insulin resistance is multi factorial, one factor associated with reduced insulin action is enhanced activity of the serine/threonine kinase glycogen synthase kinase-3 (GSK-3) in skeletal muscle, liver, and adipose tissue. GSK-3 is involved in numerous cellular functions, including glycogen synthesis, protein synthesis, gene transcription, and cell differentiation. Evidence from muscle and fat cell lines and in skeletal muscle from a variety of obese rodent models and from type 2 diabetic humans supports a role of GSK-3 over activity in the development of insulin resistance of glucose transport and glycogenesis. Studies utilizing highly selective GSK-3 inhibitors indicate that GSK-3 over activity in obesity is associated with enhanced IRS-1 serine phosphorylation and defective IRS-1-dependent signaling, ultimately resulting in reduced GLUT-4 translocation and glucose transport activity in skeletal muscle. A role of GSK-3 over activity in the
exaggerated hepatic glucose production of type 2 diabetes has also been reported. Recent studies have demonstrated that oxidative stress, resulting from enhanced exposure to oxidants, causes impaired insulin signaling and insulin resistance of skeletal muscle glucose transport, in part due to reduced suppression of GSK-3 activity and increased IRS-1 Ser(307) phosphorylation. The evidence to date supports an important role of GSK-3 dysfunction in the multifactorial etiology of insulin resistance in skeletal muscle. GSK-3 remains an important target for interventions designed to improve insulin action in obesity-associated insulin resistance and type 2 diabetes.

3. Kaidanovich O et al. reported that Glycogen synthase kinase-3 (GSK-3) is a ubiquitous cytosolic serine/threonine protein kinase that has been implicated in multiple receptor-mediated intracellular processes. Its unique feature, which distinguishes it from other protein kinases, is that it is constitutively active in resting conditions and acts as a suppressor of signalling pathways. The fact that the function of two key targets of insulin action, glycogen synthase and insulin receptor substrate-1, are suppressed by GSK-3, as well as the fact that GSK-3 activity is higher in diabetic tissues, makes it a promising drug discovery target for insulin resistance and Type 2 diabetes. Thus, the development of GSK-3 inhibitors has received attention as an attempt to control both the spread of the disease and its severity.

4. Bastaki et al., reported a review on diabetes mellitus and its treatment. Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. It is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025.

5. Ballard et al., reported Pathophysiology of Diabetes. Diabetes is a chronic metabolic disorder in which the body cannot metabolize carbohydrates, fats, and proteins because of a lack of, or ineffective use of, the hormone insulin. Diabetes is classified into three primary types that are different disease entities but share the symptoms and complications of hyperglycemia (high blood glucose).

6. Gerald et al., reported Cellular mechanisms of insulin resistance. It is estimated that by the year 2020 there will be approximately 250 million people affected by type 2 diabetes mellitus worldwide (1). Although the primary factors causing this disease
are unknown, it is clear that insulin resistance plays a major role in its development. Evidence for this comes from (a) the presence of insulin resistance 10-20 years before the onset of the disease (b) cross-sectional studies demonstrating that insulin resistance is a consistent finding in patients with type 2 diabetes and (c) prospective studies demonstrating that insulin resistance is the best predictor of whether or not an individual will later become diabetic.

7. Modi et al.\(^7\) reported an update of pharmacologic interventions for diabetes with practical overview of the new drug options, new insulin analogues. Pharmacology, clinical efficacy, safety, dosing, cost, with specific examples of each and their background and side effects used to achieve tight glucose control. These agents have distinct characteristics that help in their selection for the treatment of type 1 and type 2 diabetes. The most potent analogue showed a significant increase in liver glycogen level at the 5, 15, and 25 mg/kg dose levels, in vivo. Pharmacophore model was built and validated using in-house database of active and inactive GSK-3β inhibitors. The GSK-3β inhibitory activity of PMHs entitles them to be potential leads for the treatment of cancer, Alzheimer’s disease, bipolar disorders, stroke, different tau pathologies, and type-2 diabetes.

8. Sarabu et al.,\(^8\) reported recent advances in therapeutic approaches to type 2 diabetes. Type-2 diabetes (T2D) affects an increasing proportion of populations of both the developed and developing parts of the world. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 17 million Americans (6.2% of the U.S. population) have diabetes, and more than one third of these are undiagnosed. Another 16 million have insulin resistance or pre-diabetes. Worldwide figures are even more staggering: in 2000 the World Health Organization (WHO) reported a worldwide incidence of 154.4 million diabetes patients. Hence,
intense efforts towards the discovery and development of more efficacious and safer diabetes therapies are underway in academic and industrial research organizations.

9. **Li et al.**, reported have been designed and synthesized as a novel class of tyrosine kinase inhibitors which exhibit selectivity toward different receptor tyrosine kinases (RTKs).

- Synthesis of oxindole for bioisosteric substitution-

![Synthesis of oxindole for bioisosteric substitution](image)

**10. Hendrik et al.**, reported recently, the serine/threonine kinase glycogen synthase kinase-3 (GSK-3) emerged as a regulator of pancreatic β-cell growth and survival. On the basis of the previous observation that GSK-3 inhibitors like 1-azakenpaullone promote β-cell protection and replication, paullone derivatives were synthesized including 1-aza-, 2-aza-, and 12-oxapaullone scaffolds. In enzymatic assays distinct 1-azapaullones were found to exhibit selective GSK-3 inhibitory activity. Within the series of 1-azapaullones, three derivatives stimulated INS-1E β-cell replication and protected INS-1E cells against glucolipotoxicity induced cell death. Cazpaullone (9-cyano-1-azapaullone), the most active compound in the protection assays, also stimulated the replication of primary β cells in isolated rat islets. Furthermore, cazpaullone showed a pronounced transient stimulation of the mRNA expression of the β cell transcription factor Pax4, an important regulator of β cell development and growth. These features distinguish cazpaullone as a unique starting point for the development of β cell regenerative agents which might be useful in the treatment of diabetes.
11. Khanfar et al.,\textsuperscript{11} reported to explore a possible molecular target of phenyl methylene hydantoin (PMH) derivatives the most potent synthetic analogue has been virtually screened against various protein kinases. Molecular modeling study has shown that PMH can be successfully docked within the binding pocket of glycogen synthase kinase-3β (GSK-3β) similar to the well-known GSK-3β inhibitor. Several phenyl methylene hydantoin derivatives showed potent in vitro GSK-3β inhibitory activity with an IC$_{50}$ range of 4-20 µM.

12. Sivaprakasama et al.,\textsuperscript{12} reported Glycogen synthase kinase-3α (GSK-3α) was recently found to be an attractive target for the treatment of Alzheimer’s disease due to its dual action in the formation of both amyloid plaques and neurofibrillary tangles. It is also a viable target for many other diseases, such as type 2 diabetes. Reported herein is a 2D-QSAR exploration of the physicochemical (hydrophobic, electronic and steric) and structural requirements among 3-anilino-4-phenylmaleimides toward GSK-3α binding.

\begin{center}
\includegraphics[width=0.7\textwidth]{structure.png}
\end{center}

13. Vats et al.,\textsuperscript{13} reported the worldwide epidemic of type 2 diabetes (NIDDM) has been stimulating the search for new concepts and targets for the treatment of this incurable disease. Most current therapies were developed in the absence of defined molecular targets. Increasing knowledge on the biochemical and cellular alterations occurring in NIDDM has led to the development of novel and potentially more effective therapeutic approaches to treat the disease. The role of peroxisome proliferator activated receptors (PPARs) in the regulation of lipid metabolism, insulin and triglycerides leads to the rational design of several PPAR agonists. However, many promising molecules, especially the dual-acting PPARγ/α, are yet to be approved due to safety issues. Meanwhile, two targets, protein tyrosine phosphatase 1B (PTP-1B) and glycogen synthase kinase-3 (GSK-3), have emerged as validated targets for treating this disease. The activity of various nonpeptidic small molecules as
well as small peptides like PTP 1B inhibitors has been studied. Likewise, GSK-3, which plays a key role in the insulin signalling pathway, has been intensely studied by various companies as a potential target for the development of antidiabetic therapies. This review focuses on PTP-1B and GSK-3 inhibitors studied until now. Role of GSK-3 in insulin receptor signalling & present status of GSK-3 inhibitors.

14. **Nikoulina et al.,** reported the potential role of GSK-3 in insulin resistance and found that Glycogen synthase (GS) activity is reduced in skeletal muscle of type 2 diabetes, despite normal protein expression, consistent with altered GS regulation. Glycogen synthase kinase-3 (GSK-3) is involved in regulation (phosphorylation and deactivation) of GS, were studied in biopsies of vastus lateralis from type 2 and non-diabetic subjects before and after 3-h hyperinsulinemic (300 mU·m⁻²·min⁻¹)-euglycemic clamps.

15. **Murakami et al.,** reported the improvement of metabolic disorders in genetically obese rodents by M16209 (1-(3-bromobenzofuran-2-ylsulfonyl)hydantoin), an antidiabetic agent, in genetically obese Zucker fa/ fa rats and C57BL/6J ob/ob mice is due to amelioration of insulin resistance in peripheral tissues.

16. **Castro et al.,** reported Non-ATP competitive glycogen synthase kinase 3β (GSK-3β) inhibitors: Study of structural requirements for thiadiazolidinone derivatives. The basic skeleton of 1,2,4-thiadiazole and also one of the carbonyl groups are kept, while different modifications are introduced in positions 3 and 5, respectively. The GSK-3β activity of the new thiadiazole derivatives here synthesized showed IC50 values for some of the compounds in the micromolar range.
17. **Sarges et al.**,\(^ {17}\) reported a series of novel tetrahydroquinoline-derived spiro-hydantoin compounds are useful in therapy for the control of certain chronic diabetic complications.

18. **Sheelagh et al.**,\(^ {18}\) reported generation of the mouse knockout of GSK3\(β\), as well as studies in neurons, also suggest an important role in apoptosis. The substrate specificity of GSK3 is unusual in that efficient phosphorylation of many of its substrates requires the presence of another phosphorylated residue optimally located four amino acids C-terminal to the site of GSK3 phosphorylation. Recent experiments, including the elucidation of its three-dimensional structure, have enhanced our understanding of the molecular basis for the unique substrate specificity of GSK3. Insulin and growth factors inhibit GSK3 by triggering its phosphorylation, turning the N-terminus into a pseudosubstrate inhibitor that competes for binding with the ‘priming phosphate’ of substrates. -Regulation of GSK3 by insulin and growth factors.

19. **Laurent et al.**,\(^ {19}\) reported potential sites for inhibition of glycogen synthase kinase 3 (GSK-3). Most kinase inhibitors act by competition with either ATP or metal-binding sites that are involved directly in the catalytic process. However, small-molecular-weight compounds might regulate GSK-3 activity by inhibiting the protein–protein interactions that are necessary for binding of substrate [the primed phosphorylated serine binding area and the docking protein (axin and presenilin)], by modulating the Tyr216 (GSK-3\(β\)) and Tyr279 (GSK-3\(α\)) activation sites and the Ser9
(GSK-3β) and Ser21 (GSK-3α) inhibition sites, and by interfering with the intracellular targeting domain of GSK-3. Inhibition of the interaction between the docking protein and the priming kinase might change the substrate specificity of GSK-3. Potential site for inhibition of glycogen synthase kinase-3.

20. Murava et al., reported the Elucidating Substrate and Inhibitor Binding Sites on the Surface of GSK-3β and the Refinement of a Competitive Inhibitor. Computational modeling of new L803 variants predicted that inhibition would be strengthened by adding contacts with Phe93 or by increasing the hydrophobic content of the peptide.

21. Hendrik et al., reported recently, the serine/threonine kinase glycogen synthase kinase-3 (GSK-3) emerged as a regulator of pancreatic β-cell growth and survival. On the basis of the previous observation that GSK-3 inhibitors like 1-azakenpaullone promote β-cell protection and replication, paullone derivatives were synthesized including 1-aza-, 2-aza-, and 12-oxapaullone scaffolds. In enzymatic assays distinct 1-azapaullones were found to exhibit selective GSK-3 inhibitory activity. Within the series of 1-azapaullones, three derivatives stimulated INS-1E β-cell replication and protected INS-1E cells against glucolipotoxicity induced cell death. Cazpaullone (9-cyano-1-azapaullone), the most active compound in the protection assays, also stimulated the replication of primary β cells in isolated rat islets. Furthermore, cazpaullone showed a pronounced transient stimulation of the mRNA expression of the β cell transcription factor Pax4, an important regulator of β cell development and growth. These features distinguish cazpaullone as a unique starting point for the development of β cell regenerative agents which might be useful in the treatment of diabetes.

- Structures of established GSK-3 inhibitors:

![Structures of established GSK-3 inhibitors](image)

Kenpaullone – R¹ = Br
Alsterpaullone - R¹ = NO₂
22. Ana et al.,\textsuperscript{22} reported Glycogen Synthase kinase 3α(GSK-3α) has a central role in Alzheimer’s disease (AD). Selective inhibitors which avoid hyperphosphorylation may represent an effective therapeutically approach to the AD pharmacotherapy and other neurodegenerative disorders. Here, we describe the synthesis, biological evaluation, and SAR of the small heterocyclic thiazolidinone (TDZD) as the first non-ATP competitive inhibitor of GSK-3α. Their synthesis is based on the reactivity of sulfenyl chlorides. In GSK-3α assays, TDZD derivatives showed IC\textsubscript{50} values in the micro molar range, whereas in other protein kinases assays they were devoid of any inhibitory activity. SAR studies allowed the identification of the key structural features. Finally, a possible enzymatic binding mode is proposed.-Synthesis of Thiazolidinedione & rhodadine Nucleus: for bioisoesteric substitution.

23. Irina et al.,\textsuperscript{23} reported recent studies have demonstrated that glycogen synthase kinase 3β(GSK-3β) is over expressed in human colon and pancreatic carcinomas, contributing to cancer cell proliferation and survival. Here, we report the design, synthesis, and biological evaluation of benzofuran-3-yl-(indol-3-yl) maleimides, potent GSK-3β inhibitors. Some of these compounds show picomolar inhibitory activity toward GSK-3β and an enhanced selectivity against cyclin-dependent kinase 2 (CDK-2). Selected GSK-3β inhibitors were tested in the pancreatic cancer cell lines MiaPaCa-2, BXPC-3, and HupT3.

Reagents and conditions:

(a) MeI, NaH, DMF; (b)EtO\textsubscript{2}CCOCl, Et\textsubscript{2}O; (c)Ph\textsubscript{3}PdCH\textsubscript{2}CO\textsubscript{2}Et, Toluene, 110ºC; (d) NH\textsubscript{3}/MeOH; (e) t-BuOK, THF.
24. Francis et al., 24 reported Glycogen synthase kinase 3 regulates glycogen synthase, the rate-determining enzyme for glycogen synthesis. Liver and muscle glycogen synthesis is defective in type 2 diabetics, resulting in elevated plasma glucose levels. Inhibition of GSK-3 could potentially be an effective method to control plasma glucose levels in type 2 diabetics. Structure-activity studies on an N-phenyl-4-pyrazolo [1,5-b] pyridazin-3-ylpyrimidin-2-amine series have led to the identification of potent and selective compounds with good cellular efficacy. Molecular modeling studies have given insights into the mode of binding of these inhibitors. Since the initial leads were also potent inhibitors of CDK-2/CDK-4, an extensive SAR was performed at various positions of the pyrazolo [1,5-b] pyridazin core to afford potent GSK-3 inhibitors that were highly selective over CDK-2. In addition, these inhibitors also exhibited very good cell efficacy and functional response. A representative example was shown to have good oral exposure levels, extending their utility in an in vivo setting. These inhibitors provide a viable lead series in the discovery of new therapies for the treatment of type 2 diabetes.

-N-Phenyl-4-pyrazolo [1,5-b] pyridazin-3-ylpyrimidin-2-amines:

Type of Substitutions:
R= H, CH₃, R₂=H, cycloalkyl, R₃=H, R₅=H, O(CH₂)₂OCH₃, R₆= H.

25. Ana et al., 25 reported the 2, 4-disubstituted thiadiazolidinone (TDZD) are described as the first ATP non-competitive GSK-3 inhibitors. Following an SAR study about TDZD, different structural modifications in the heterocyclic ring aimed to
test the influence of each heteroatom on the biological study are here reported here. Various compounds such as hydantoins, dithiazolidindiones, rhodanines, maleimides, and triazoles were synthesized and screened as GSK-3 inhibitors. After an extensive SAR study among these different heterocyclic families, TDZDs have been revealed as a privileged scaffold for the selective inhibition of GSK-3. A CoMFA analysis was also performed highlighting the molecular electrostatic field interaction in the interaction of TDZDs with GSK-3. Moreover, first mapping studies indicate two binding modes which in turn might imply relevant differences in the mechanism that underlies the inhibitory activity of TDZDs.-The structural differences in the hetero aromatic rings of the different classes of compounds considered.

26. Konstantina et al.,\textsuperscript{26} reported Glycogen synthase kinase-3 (GSK-3) is a key enzyme involved in numerous physiological events and in major diseases, such as Alzheimer’s disease, diabetes, and cardiac hypertrophy. Indirubins are bis-indoles that
can be generated from various natural sources or chemically synthesized. While rather potent and selective as GSK-3 inhibitors, most indirubins exhibit low water solubility. To address the issue of solubility, we have designed novel analogues of 6-bromo-indirubin-3′-oxime with increased hydrophilicity based on the GSK 3/indirubins cocrystal structures. The new derivatives with an extended amino side chain attached at position 3′ showed potent GSK-3 inhibitory activity, enhanced selectivity, and dramatically increased water solubility. Furthermore, some of them displayed little or no cytotoxicity. The new indirubins inhibit GSK-3 in a cellular reporter model. They alter the circadian period measured in rhythmically expressing cell cultures, suggesting that they might constitute tools to investigate circadian rhythm regulation.

-Soluble 3′,6-Substituted Indirubins:

27. Panagiotis et al., reported Pharmacological inhibitors of glycogen synthase kinase-3 (GSK-3) and cyclin dependent kinases have a promising potential for applications against several neurodegenerative diseases such as Alzheimer’s disease. Indirubins, a family of bis-indoles isolated from various natural sources, are potent inhibitors of several kinases, including GSK-3. Using the co-crystal structures of various indirubins with GSK-3β, CDK2 and CDK5/p25, we have modelled the binding of indirubins within the ATP-binding pocket of these kinases. This modelling approach provided some insight into the molecular basis of indirubins’ action and selectivity and allowed us to forecast some improvements of this family of bis-indoles as kinase inhibitors. Predicted molecules, including 6-substituted and 5,6-disubstituted indirubins, were synthesized and evaluated as CDK and GSK-3 inhibitors. Control, kinase-inactive
indirubins were obtained by introduction of a methyl substitution on N1. -synthesis of isatin nucleus from aniline derivatives:

\[
\text{X} = \text{H, Br, I, F}, \quad \text{Y} = \text{H, Cl, CH}_3.
\]

Reagents:
(a) Chloral hydrate, Na$_2$SO$_4$, H$_2$NOH.HCl, H$_2$O, H$^+$(b) H$_2$SO$_4$

28. Thomas et al.,$^{28}$ reported Glycogen synthase kinase-3 (GSK3) is involved in signaling from the insulin receptor. Inhibitors of GSK3 are expected to affect lowering of plasma glucose similar to insulin, making GSK3 an attractive target for the treatment of type 2 diabetes. Herein we report the discovery of a series of potent and selective GSK3 inhibitors. -Substituted-3-Imidazo[1,2-a]pyridin-3-yl-4-(1,2,3,4-tetrahydro-[1,4]diazepino [6,7,1 hi]indol-7-yl)pyrrole-2,5-diones:

29. Preben et al.,$^{29}$ reported a novel class of GSK-3 inhibitors with favourable water solubility was identified in a HTS screen. SAR studies identified bioisoesteric
structural moieties in this class of compounds. The compounds were tested in a GSK-3 inhibition assay at 100 µM ATP giving IC₅₀’s in the range from 0.1 to 10 µM. The compounds are ATP competitive inhibitors. They modulate glycogen metabolism and stimulate the accumulation of intracellular α-catenin in whole cell assays with EC₅₀’s in the range from 2 to 18 µM and 4.5-44 µM, respectively. For selected compounds, only a 10-fold lower potency was obtained in cellular assays compared to the potency obtained for inhibition of the isolated enzyme, reflecting a good cell permeability of this compound class. At 10 µM of test compound a 3-fold stimulation of the glycogen synthesis in rat soleus muscle was obtained compared to the level of glycogen synthesis observed at 0.2 nM insulin. This stimulation of glycogen synthesis is comparable to the maximal stimulation by insulin itself.-1-(4-Aminofurazan-3-yl)-5-dialkylaminomethyl-1H-[1,2,3]triazole-4-carboxylic acid derivatives:

30. Andrew et al.,³⁰ reported 1-15N-L-Tryptophan (1-15N-L-Trp) was synthesized from 15N-aniline by a Sandmeyer reaction, followed by cyclization to isatin, reduction to indole with LiAlH₄, and condensation of the 15N-indole with L-serine, catalyzed by tryptophan synthase.-Synthesis of isatin

\[
\begin{align*}
\text{NH}_2 & \xrightarrow{\text{Cl}_{3}C\text{CHO}} \text{NH}_2 \xrightarrow{\text{H}_2\text{SO}_4} \text{NH}_2 \xrightarrow{\text{LiAlH}_4} \text{NH}_2
\end{align*}
\]
31. Robert et al.,\textsuperscript{31} reported the novel regiospecific and general reduction of 5-benzylidene-2,4thiazolidinediones and 5-benzylidene-4-oxo-2-thiazolidinethiones to the corresponding 5-benzyl derivatives has been accomplished using lithium borohydride in pyridine and tetrahydrofuran. Sodium borohydride and lithium chloride can also be used under these conditions, which represents a cheaper alternative to lithium borohydride.

-Preparation and reduction of 5-benzylidenethiazolidin-2,4-diones and 4-oxothiazolidin-2-thiones:

\[
\begin{array}{cccc}
\text{R}^1 & \text{R}^2 & \text{R}^3 & \text{X} \\
\text{H} & \text{H} & \text{H} & \text{H} & \text{O} \\
\text{H} & \text{H} & \text{F} & \text{H} & \text{O} \\
\text{H} & \text{H} & \text{Br} & \text{H} & \text{O} \\
\text{H} & \text{H} & \text{OCH}_3 & \text{H} & \text{O} \\
\text{H} & \text{H} & \text{H} & \text{CH}_3 & \text{O} \\
\text{H} & \text{H} & \text{H} & \text{CH}_3 & \text{S} \\
\text{H} & \text{t-butyl} & \text{OH} & \text{H} & \text{O} \\
\text{CH}_3 & \text{H} & \text{H} & \text{H} & \text{O} \\
\end{array}
\]
32. Patel et al., reported dysregulation of the protein kinase glycogen synthase kinase 3 (GSK-3) has been implicated in the development of type 2 diabetes mellitus. GSK-3 protein expression and kinase activity are elevated in diabetes, while selective GSK-3 inhibitors have shown promise as modulators of glucose metabolism and insulin sensitivity. To assess the potential role of GSK-3β in insulin function, a conditional gene-targeting approach whereby mice in which expression of GSK-3β was specifically ablated within insulin-sensitive tissues were generated was undertaken.

33. Artur et al., reported a palladium-catalyzed three-component synthesis of 3-(diaryl)methyleneindolin-2-ones has been developed. A sequence of intermolecular N arylation/intermolecular carbopalladation/C–H activation/C–C bond formation was realized in a one-pot fashion allowing the construction of one C–N bond and two C–C bonds by way of three distinct catalytic cycles. Palladium-catalyzed three-component synthesis of oxindoles for bioisosteric substitution:

- Reaction and condition:
  i) Pd, L, CS₂CO₃:dioxane, 100°C.
  ii) PhI in DMF, 110°C.

34. Torsten et al., reported the radio synthesis and radio pharmacological evaluation of 3-[40-[18F] fluorobenzylidene] indolin-2-one, a derivative of tyrosine kinase inhibitor SU5416, is described. The radio synthesis was accomplished by Knoevenagel condensation of 4-[18F] fluorobenzaldehyde with oxindole in a remotely
controlled synthesis module. The reaction conditions were optimized through screening the influence of different bases on the radiochemical yield.

-synthesis of phenylmethyleneindoline-2-one derivatives: \( R = \text{NO}_2 \)

- Reagent & conditions: (i) EtOH, piperidine, reflux; (ii) 4-nitrobenzaldehyde, EtOH, piperidine, reflux; (iii) 4-dimethylamino-benzaldehyde, EtOH, reflux;

35. Bramson et al.,\textsuperscript{35} reported substituted isatins typically were prepared via the classical Sandmeyer Reaction involving conversion of the substituted aniline with hydroxylamine and chloral hydrate to the intermediate isonitrosoacetanilide, followed by cyclization in either concentrated sulfuric acid or boron trifluoride etherate. Oxindoles were obtained, either directly from the corresponding isatin by Wolf Kishner reduction or alternatively from the substituted aniline via the Gassman synthesis.

-synthesis of isatin:

Reagent & Conditions:
(i) chloral hydrate, \( \text{NH}_2\text{OH HCl, Na}_2\text{SO}_4, \text{EtOH/ HCl(aq)} \); (ii) \( \text{H}_2\text{SO}_4(\text{conc.}) \) or \( \text{BF}_3\text{OEt}_2 \); (iii) \( (\text{BuOCO})_2\text{O, THF} \); (iv) t-BuLi, THF; (v) \( \text{EtO}_2\text{CCO}_2\text{Et, THF} \); (vi) \( \text{HCl(aq)} \); (vii) HCl, EtOH.
36. Peat *et al.*, reported a novel series of [1-(1H-benzimidazol-7-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]arylhydrazones was synthesized and shown to potently inhibit glycogen synthase kinase-3 (GSK-3). In light of detailed structure–activity relationships and structural knowledge of the GSK-3 binding pocket, a benzimidazole substituent was incorporated onto the pyrazolopyrimidine core resulting in improved potency over previous analogs. More importantly, these derivatives show low nanomolar efficacy for stimulating glycogen synthesis in vitro and therefore may be useful in the treatment of type 2 diabetes mellitus.

37. Koryakova *et al.*, reported synthesis, biological evaluation, and SAR dependencies for a series of novel aryl and heteroaryl substituted N-[3-(4-phenylpiperazin-1-yl) propyl]-1, 2, 4-oxadiazole-5-carboxamide inhibitors of GSK-3β kinase are described. The inhibitory activity of the synthesized compounds is highly dependent on the character of substituents in the phenyl ring and the nature of terminal heterocyclic fragment of the core molecular scaffold. The most potent compounds from this series contain 3,4-di-methyl or 2-methoxy substituent’s within the phenyl ring and 3-pyridine fragment connected to the 1,2,4-oxadiazole heterocycle. These compounds selectively inhibit GSK-3β kinase with IC<sub>50</sub> value of 0.35 and 0.41 µM, respectively.
38. O’Neill et al.,\textsuperscript{38} reported the hydroxyl propyl-substituted 7-azaindolylmaleimide template was first used to screen different heteroaryls attached to the maleimide. Replacement of hydroxy propyl with different chain lengths and different functional groups were studied next. Many compounds synthesized were demonstrated to have high potency at GSK 3β, good GS activity in HEK293 cells and good to excellent metabolic stability in human liver microsomes.

39. Witherington et al.,\textsuperscript{39} reported a novel series of pyrazolo [3,4-b] pyridines have been identified that are potent inhibitors of glycogen synthase kinase-3 (GSK-3).

40. Testard et al.,\textsuperscript{40} reported in an effort to identify new protein kinase inhibitors with increased potency and selectivity, we have developed the microwave-assisted synthesis of thiazolo [5, 4-f] quinazolin-9-ones. The effects of eighteen derivatives on CDK1/cyclin B, CDK5/p25, and GSK-3 were investigated. Several turned out to inhibit GSK-3 in the micro molar range. Molecular modeling studies suggest that the most selective GSK-3 inhibitors 7a-d bind into the ATP-binding site through a key
hydrogen bond interaction with Val135 and target the specific hydrophobic back pocket of the enzyme.

41. Perez et al., 41 reported Thienyl halomethyl ketones, whose chemical, biological, and pharmaceutical data are here reported, are the first irreversible inhibitors of GSK-3β described to date. Their inhibitory activity is likely related to the cysteine residue present in the ATP-binding site, which is proposed as a relevant residue for modulation of GSK-3 activity. The good cell permeability of the compounds allows them to be used in different cell models. Overall, the results presented here support the potential use of halomethylketones as pharmacological tools for the study of GSK-3β functions and suggest a new mechanism for GSK-3β inhibition that may be considered for further drug design. First compounds used for the GSK-3β inhibition screening with their experimental IC₅₀ values:
42. Maeda et al.,\(^{42}\) reported modeling studies of a furo[2,3-d]pyrimidine GSK-3 hit compound 1 superimposed onto the X-ray crystal structure of a legacy pyrazolo[3,4-c]pyridazine GSK-3 inhibitor 2 led to the identification of 4-acylamino-6-arylfuro[2,3-d]pyrimidine template 3. Synthesis of analogues based on template 3 has resulted in a number of potent and selective GSK-3β inhibitors.

![Chemical Structures](image1.png)

43. Zhang et al.,\(^{43}\) reported novel bis (indolyl) maleimide pyridinophanes were prepared by cobalt-mediated [2+2+2] cycloaddition of an appropriate a, x-diyne with an N, N-dialkylcyanamide. These macro cyclic heterophanes were found to be potent, selective inhibitors of glycogen synthase kinase-3β. An X-ray structure of a co-crystal of GSK-3β and 3 (IC\(_{50}\) = 3 nM) depicts the hydrogen bonding and hydrophobic interactions in the ATP-binding pocket of this serine/threonine protein kinase.

![Chemical Structures](image2.png)

44. Miyazaki et al.,\(^{44}\) reported 4-Amino-5, 6-diaryl-furo [2, 3-d] pyrimidines have been identified as inhibitors of glycogen synthase kinase-3β (GSK-3β). One representative derivative, 4-amino-5-(4-(benzenesulfonylamino)-phenyl)-6-(3-pyridyl)-furo [2,3-d] pyrimidine exhibited potent GSK-3β inhibitory activity in low nanomolar level of IC\(_{50}\). The binding mode was proposed from a docking study. Binding modes of the VEGFR2/Tie-2 inhibitor 4-amino-5,6-diaryl-furo[2,3-

45. Beauchardet al.,45 reported in an effort to identify new pharmacological inhibitors of disease-relevant protein kinases with increased potency and selectivity we synthesized and evaluated new 5-substituted indirubins. The effects of 34 indirubin derivatives on CDK1/cyclin B, CDK5/p25, and GSK-3, as well as on SH-SY5Y human neuroblastoma cell survival, were investigated.

46. Masiello et al.,46 reported type 2 diabetes is increasingly viewed as a disease of insulin deficiency due not only to intrinsic pancreatic β-cell dysfunction but also to reduction of β-cell mass. It is likely that, in diabetes-prone subjects, the regulated β-cell turnover that adapts cell mass to body’s insulin requirements is impaired, presumably on a genetic basis. We still have a limited knowledge of how and when this derangement occurs and what might be the most effective therapeutic strategy to preserve β-cell mass. The animal models of type 2 diabetes with reduced β-cell mass
Chapter 2

Literature Survey

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described in this review can be extremely helpful (a) to have insight into the mechanisms underlying the defective growth or accelerated loss of β-cells leading to the β-cell mass reduction; (b) to investigate in prospective studies the mechanisms of compensatory adaptation and subsequent failure of a reduced β-cell mass. Furthermore, these models are of invaluable importance to test the effectiveness of potential therapeutic agents that either stimulate β-cell growth or inhibit β-cell death.

47. Smalley et al., reported a set of novel heterocyclic pyrimidyl hydrazones has been synthesized as inhibitors of glycogen synthase kinase-3 (GSK-3) with the most active exhibiting low nanomolar activity. Quantum mechanical calculations indicate that of the conformational factors that could determine binding affinity, the planarity of the phenyl ring in relation to the central core and the conformation of the hydrazone chain may be the most influential.

48. Hamann et al., reported Manzamine A and related derivatives isolated from a common Indonesian sponge, Acanthostrongylophora, have been identified as a new class of GSK-3β inhibitors. The semi synthesis of new analogues and the first structure–activity relationship studies with GSK-3β are also reported. Moreover, manzamine A proved to be effective in decreasing tau hyperphosphorylation in human neuroblastoma cell lines, a demonstration of its ability to enter cells and interfere with tau pathology. Inhibition studies of manzamine A against a selected panel of five different kinases related to GSK-3β, specifically CDK-1, PKA, CDK-5, MAPK, and GSK-3α, show the specific inhibition of manzamine A on GSK-3β and CDK-5, the two kinases involved in tau pathological hyperphosphorylation. These results suggest that manzamine A constitutes a promising scaffold from which more potent and selective GSK-3 inhibitors could be designed as potential therapeutic agents for Alzheimer’s disease.
Reagents:
(i) Cl₂, hexane, N₂, -15°C.
(ii) R'-N=C=O, hexane, N₂, room temperature.
(iii) Air, room temperature.

49. Mohammad A. Khanfar et al. ⁴⁹ reported that dysregulation of glycogen synthase kinase (GSK-3β) is implicated in the pathophysiology of many diseases, including type-2 diabetes, stroke, Alzheimer’s, and others. A multistage virtual screening strategy designed so as to overcome known caveats arising from the
considerable flexibility of GSK-3β yielded, from among compounds in our in-house
database and two commercial databases, new GSK-3β inhibitors with novel scaffold
structures. The two most potent and selective validated hits, a 2-anilino-5-phenyl-
1,3,4-oxadiazole (24) and a phenylmethylene hydantoin (28), both exhibited
nanomolar affinity and selectivity over CDK2 and were potent enough for direct in
vivo validation. Both were able to cause significant increases in liver glycogen
accumulation in dose-dependent fashion.

\[\text{Diaa T. A. Youssef et al.}^{50}\text{ reported that}\]

In the course of our continuing efforts to identify bioactive secondary metabolites from Red Sea marine invertebrates, they
investigated the sponge Hemimycale arabica. The antimicrobial fraction of an organic
extract of the sponge afforded two new hydantoin alkaloids, hemimycalins A and B (2
and 3), together with the previously reported compound (Z)-5-(4-
hydroxybenzylidene)imidazolidine-2,4-dione (1). The structures of the compounds
were determined by extensive 1D and 2D NMR (COSY, HSQC and HMBC) studies
and high-resolution mass spectral determinations. Hemimycalins A (2) and B (3)
represent the first examples of the natural N-alkylated hydantoins from the sponge
Hemimycale arabica.

51. \textbf{Goutam Ghosh Choudhary}^{51}\text{ reported that High glucose (30 mM) and high
insulin (1 nM), pathogenic factors of type 2 diabetes, increased mRNA expression and
synthesis of laminin beta1 and fibronect in after 24 h incubation in kidney proximal
tubular epithelial (MCT) cells. It is tested that the inactivation of glycogen synthase
kinase 3beta (GSK 3beta) by high glucose and high insulin induces increase in
synthesis of laminin beta1 via activation of eIF2Bepsilon. Both high glucose and high
insulin induced Ser9 phosphorylation and inactivation of GSK 3beta at 2 h that lasted
for up to 48 h. This was associated with dephosphorylation of eIF2Bepsilon and}
eEF2, and increase in phosphorylation of 4E-BP1 and eIF4E. Expression of kinase-dead mutant of GSK 3beta or constitutively active kinase led to increased and diminished laminin beta1 synthesis, respectively.

52. Henriksen EJ reported that Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase with important roles in the regulation of glycogen synthesis, protein synthesis, gene transcription, and cell differentiation in various cell types. An emerging body of evidence has implicated GSK-3 in the multifactorial etiology of skeletal muscle insulin resistance in obese animal models and in obese human type 2 diabetic subjects. Overexpression and over activity of GSK-3 in skeletal muscle of rodent models of obesity and obese type 2 diabetic humans are associated with an impaired ability of insulin to activate glucose disposal and glycogen synthase. New insights into the importance of GSK-3 as a regulator of insulin action on glucose transport activity in muscle have come from studies utilizing selective and sensitive inhibitors of GSK-3.

53. Henriksen EJ reported that Insulin resistance of glucose transport and metabolism in insulin-sensitive tissues is a primary defect leading to the development of type 2 diabetes. GSK-3 is involved in numerous cellular functions, including glycogen synthesis, protein synthesis, gene transcription, and cell differentiation. Evidence from muscle and fat cell lines and in skeletal muscle from a variety of obese rodent models and from type 2 diabetic humans supports a role of GSK-3 overactivity in the development of insulin resistance of glucose transport and glycogenesis.

54. Nikoulina SE reported that Glycogen synthase (GS) activity is reduced in skeletal muscle of type 2 diabetes, despite normal protein expression, consistent with altered GS regulation. Glycogen synthase kinase-3 (GSK-3) is involved in regulation (phosphorylation and deactivation) of GSK.

55. Kunal M. Gokhale et al. reported that Glycogen Synthase Kinase (GSK-3) is a key enzyme involved in glycogen metabolism, protein synthesis, etc and overexpression of GSK-3 in skeletal muscle of humans is associated with impaired ability of insulin to activate glucose disposal leading to development of type-2 diabetes. Studies have demonstrated that selective and sensitive inhibition of GSK-3 causes improvements in insulin stimulated glucose transport activity. Identifying the binding sites and selectively targeting GSK-3 with GSK-3 inhibitors may emerge as a new strategy for the treatment of diabetes.
56. Issabel Dorronsoro et al. Glycogen Synthase Kinase (GSK-3) is a key enzyme involved in glycogen metabolism, protein synthesis, etc. and overexpression of GSK-3 in skeletal muscle of humans is associated with impaired ability of insulin to activate glucose disposal leading to development of type-2 diabetes. Studies have demonstrated that selective and sensitive inhibition of GSK-3 causes improvements in insulin stimulated glucose transport activity. Identifying the binding sites and selectively targeting GSK-3 with GSK-3 inhibitors may emerge as a new strategy for the treatment of diabetes.

57. Oksana Kaidanovich-Beilin and Hagit Eldar-Finkelman reported that Glycogen synthase kinase-3 (GSK-3) is critically involved in insulin signaling, and its selective inhibition may present a new therapy for treatment of insulin resistance and type 2 diabetes. The current studies were designed to examine the impact of long-term in vivo inhibition of GSK-3 and its effects in the specific tissues. Ob/ob mice were treated daily with one dose (400 nmol, i.p.) of a selective GSK-3 peptide inhibitor, L803mts, for 3 weeks. Treatment with L803-mts reduced blood glucose levels, improved glucose tolerance, and prevented elevation of hyperglycemia with age. However, L803-mts did not affect either body weight or food consumption and was not toxic, as judged by histopathology and blood chemistry analyses. Consistent with these results, L803-mts suppressed mRNA levels of hepatic phosphoenolpyruvate carboxykinase (PEPCK) (50%) and increased hepatic glycogen content by 50%.

58. Haomeng Wang et al. reported that A series of hydantoin derivatives were designed and synthesized about 25-30% overall yields. Two of the six newly synthesized compounds, compound 3, 5 have not been reported before. Compounds 2-6 were obtained by Aldol reaction and those structures were confirmed by 1H and 13C NMR. All the newly synthesized derivatives were subjected to evaluate their cytotoxic properties against human tumor cell lines, HepG2. Results indicated that compounds 2 and 4 exhibited significant anti-tumor activities against liver cancer (HepG2) cell lines. Among, compound 2 with the IC50 values of 3.37 µM against cancer cell lines HepG2.