A REVIEW ON MOLECULAR MODELING AND STRUCTURE BASED DESIGN OF GSK-3 INHIBITORS

Mrs.Sravani Devi. Kakara, Harika.Pudi,Hema Latha Surya. Ponnamati, Sowjanya.Pantham, Venkata Lakshmi. Pilla, Srivalli Naga Tejaswini.Pedavegi,Dr.N.V.V. Jagan Mohan Reddy,Dr. D. Narendra.
Sravanidevi82@gmail.com

ABSTRACT:

Glycogen Synthase Kinase-3 (GSK-3) is a multifunctional serine/threonine protein kinase that regulates diverse cellular processes, including glycogen metabolism, cell proliferation, apoptosis, neuronal development, and gene expression. Dysregulation of GSK-3 has been implicated in several pathological conditions, such as Alzheimer's Disease, Parkinson's Disease, Type 2 Diabetes, cancer, and inflammatory diseases, making it an attractive therapeutic target. However, the development of selective GSK-3 inhibitors remains challenging because of the high structural conservation of kinase ATP-binding sites and the close homology between GSK-3α and GSK-3β isoforms. Structure-based drug design has emerged as a powerful strategy to overcome these limitations and facilitate the discovery of potent and selective inhibitors. This review summarizes recent advances in structure-based approaches employed in GSK-3 inhibitor design, including X-ray crystallography, molecular docking, virtual screening, pharmacophore fragment-based drug design, and molecular dynamics simulations. Detailed structural insights into the ATP-binding pocket, substrate recognition regions, and allosteric binding sites have enabled the rational optimization of inhibitor potency, selectivity, and pharmacokinetic properties. In addition, computational techniques and artificial intelligence-assisted drug discovery have accelerated the identification of novel chemical scaffolds and improved prediction of ligand–protein interactions. The integration of structural biology with medicinal chemistry has led to the development of ATP-competitive, substrate-competitive, and allosteric GSK-3 inhibitors with enhanced selectivity profiles. Continued advances in structure-guided drug design are expected to support the development of safer and more effective GSK-3-targeted therapeutics for the treatment of neurodegenerative, metabolic, and oncological disorders.

KEY WORDS:

GSK-3, structure-based drug design, selective inhibitors, molecular docking, virtual screening, molecular dynamics, kinase inhibitors, drug discovery.

1.INTRODUCTION:

Glycogen synthase kinase-3 (GSK-3) is a highly conserved serine/threonine protein kinase that plays a pivotal role in numerous cellular processes including glycogen metabolism, cell proliferation, differentiation, apoptosis, and signal transduction pathways [1–3]. Two isoforms of GSK-3, namely GSK-3α and GSK-3β, have been identified in mammals, sharing substantial sequence homology while exhibiting distinct physiological functions [4,5]. Among these isoforms, GSK-3β has attracted considerable attention because of its involvement in the pathogenesis of several chronic disorders such as Alzheimer’s disease, Parkinson’s disease, type 2 diabetes mellitus, bipolar disorder, inflammatory diseases, and various cancers [6–10].

The kinase was initially discovered as a regulator of glycogen synthase activity; however, subsequent studies revealed that GSK-3 participates in a wide range of signal pathways, including W/β-catenin, PI3K/Akt, Hedgehog, Notch, and NF-κ signalpathways [11–15]. Dysregulation of these pathways contributes significantly to disease progression, making GSK-3 an attractive therapeutic target for drug discovery and development [16–18]. The broad involvement of GSK-3 in cellular homeostasis has prompted extensive efforts toward the identification of potent and selective inhibitors capable of modulating kinase activity without affecting related kinases [19–21].

Over the past two decades, numerous GSK-3 inhibitors have been developed, including ATP-competitive inhibitors, non-ATP competitive inhibitors, substrate-competitive inhibitors, and allosteric modulators [22–25]. Despite significant progress, achieving high selectivity remains a major challenge due to the highly conserved nature of the ATP-binding pocket among protein kinases [26–28]. Lack of selectivity often leads to off-target interactions, resulting in undesirable adverse effects and limited clinical success [29,30]. Consequently, structure-based drug design

(SBDD) has emerged as a powerful strategy for the rational development of selective GSK-3 inhibitors.

Structure-based drug design utilizes three-dimensional structural information obtained from X-ray crystallography, nuclear magnetic resonance spectroscopy, cryo-electron microscopy, and computational model techniques to identify key molecular interactions within the active site of target proteins [31–34]. The availability of high-resolution crystal structures of GSK-3 in complex with various inhibitors has greatly facilitated the understanding of binding modes and molecular determinants responsible for potency and selectivity [35–38]. These structural insights have enabled medicinal chemists to optimize lead compounds through rational modifications aimed at enhancing target affinity, selectivity, pharmacokinetic properties, and safety profiles [39–41].

The catalytic domain of GSK-3 contains several structurally important regions including the ATP-binding pocket, hinge region, glycine-rich loop, activation loop, and substrate recognition domain [42–44]. Structural studies have demonstrated that selective inhibitors often exploit unique interactions within these regions, particularly hydrogen-bonding interactions with hinge residues and hydrophobic contacts within adjacent binding pockets [45–47]. Furthermore, the identification of less-conserved allosteric sites has opened new avenues for the development of highly selective GSK-3 inhibitors capable of minimizing off-target kinase inhibition [48–50].

Recent advances in computational chemistry, molecular docking, pharmacophore modeling, molecular dynamics simulations, quantitative structure–activity relationship (QSAR) studies, and artificial intelligence-assisted drug design have significantly accelerated the discovery of novel GSK-3 inhibitors [51–53]. Integration of these approaches with structural biology has improved the efficiency of lead optimization and increased the probability of identifying clinically viable candidates [54]. Consequently, structure-based approaches continue to play a central role in the design and development of next-generation GSK-3 selective inhibitors with improved therapeutic potential and reduced toxicity [55].

Another important structure-based strategy involves targeting substrate recognition regions rather than the ATP-binding pocket. GSK-3 displays a distinctive substrate preference requiring

prior phosphorylation of substrates, a phenomenon known as priming. Structural investigations identified a positively charged phosphate-binding pocket responsible for recognizing primed substrates. This region contains residues such as Arg96, Arg180, and Lys205, which stabilize phosphorylated substrate motifs. Structure-guided design of substrate-competitive inhibitors aimed to mimic substrate interactions within this pocket, thereby preventing substrate binding without directly competing with

ATP. Because substrate recognition sites are generally less conserved than ATP-binding regions, inhibitors targeting these areas often exhibit superior selectivity. Computational model and crystallographic analyses have facilitated the development of substrate-mimetic compounds capable of occupying substrate recognition surfaces and disrupting enzyme-substrate interactions.

Allosteric inhibition represents another promising avenue for achieving GSK-3 selectivity. Unlike ATP-competitive inhibitors, allosteric inhibitors bind to regulatory sites distinct from the catalytic pocket, inducing conformational changes that reduce enzymatic activity. Structure-based screening approaches have identified several potential allosteric sites within GSK-3, including pockets located near the activation loop and protein-protein interaction interfaces. Molecular dynamics simulations have played a particularly important role in revealing transient binding pockets not readily observable in static crystal structures. Virtual screening campaigns targeting these cryptic pockets have yielded novel allosteric ligands capable of modulating GSK-3 activity. Since allosteric sites tend to exhibit greater structural diversity among kinases, they offer significant opportunities for developing highly selective inhibitors with reduced off-target effects.

Molecular docking has become a cornerstone of structure-based GSK-3 inhibitor discovery. Docking algorithms predict the orientation and binding affinity of small molecules within target protein structures, enabling virtual screening of large compound libraries. Researchers use docking studies to prioritize compounds for synthesis and biological testing, significantly reducing experimental costs and timelines. Advanced docking protocols incorporating receptor flexibility, solvent effects, and induced-fit mechanisms improve prediction accuracy. Docking studies have successfully identified novel inhibitor scaffolds that subsequently demonstrated potent GSK-3 inhibition in biochemical assays. When combined with pharmacophore model and machine-learning techniques, docking provides a powerful platform for discovering structurally diverse inhibitors.Molecular dynamics simulations complement crystallographic and docking studies by capturing protein flexibility and dynamic behaviour. Unlike static structures, molecular dynamics simulations reveal conformational fluctuations occurring over time, providing insights into ligand stability, binding kinetics, and allosteric communication pathways.. Simulations have demonstrated that GSK-3 undergoes subtle conformational changes influencing inhibitor binding and selectivity. Dynamic analyses help identify transient pockets, flexible loops, and energetically conformations that may serve as targets for novel inhibitors. Free-energy calculations derived from molecular dynamics trajectories further assist in predicting binding affinities and guiding lead optimization efforts.

Fragment-based drug design has also emerged as an effective structure-guided strategy for GSK-3 inhibitor development. In this approach, small molecular fragments with weak binding affinity are identified through biophysical screening methods and subsequently optimized into potent inhibitors. Structural characterization of fragment-protein complexes enables precise mapping of binding interactions and facilitates rational fragment growth or linking. Fragment-

based approaches are particularly valuable for exploring novel chemical space and discovering unconventional binding modes. Several potent GSK-3 inhibitors have originated from fragment screening campaigns supported by crystallographic and computational analyses.

Selectivity between GSK-3α and GSK-3β isoforms remains an important challenge in structure-based design. Although the catalytic domains are highly similar, subtle structural differences outside the ATP-binding pocket may permit isoform-selective inhibition. Advances in structural biology, including cryo-electron microscopy and enhanced molecular simulation techniques, have improved understanding of isoform-specific conformational be. Researchers are increasingly exploring unique regulatory domains, protein interaction surfaces, and dynamic conformational states as potential sources of selectivity.

Isoform-selective inhibitors could provide therapeutic benefits while minimizing adverse effects associated with broad GSK-3 inhibition.

2.PRINCIPLES OF BASED DRUG DESIGN:

Structure-based drug design refers to the rational development of therapeutic molecules using detailed information about the three-dimensional structure of a biological target. In the context of GSK-3 inhibitor development, SBDD involves identifying critical binding interactions within the enzyme active site and designing compounds that maximize these interactions while improving selectivity and drug-like properties. The availability of numerous crystal structures of GSK-3 in complex with inhibitors has transformed the drug discovery process by providing direct visualization of molecular recognition events. Structural information enables researchers to identify hydrogen-bond donors and acceptors, hydrophobic interactions, electrostatic contacts, and solvent-mediated interactions that contribute to binding affinity.

The typical structure-based drug design workflow begins with target structure determination, followed by virtual screening of compound libraries, molecular docking studies, lead identification, and iterative optimization using medicinal chemistry. Computational methods predict how candidate molecules fit within the binding pocket and estimate their binding energies. Structural modifications are then introduced to improve potency, selectivity, metabolic stability, and pharmacokinetic be Repeated cycles of synthesis, biological evaluation, and structural analysis gradually transform initial hits into optimized lead compounds. This rational approach significantly reduces the time and cost associated with traditional trial-and-error drug discovery methods and increases the likelihood of identifying successful clinical candidates.

2.1 X-RAY CRYSTALLOGRAPHY IN GSK-3 INHIBITOR DESIGN

X-ray crystallography has been one of the most influential technologies in the development of GSK-3 inhibitors. Crystal structures provide atomic-level information regarding protein–ligand interactions and reveal how inhibitors occupy the ATP-binding pocket. The first GSK-3 crystal structures allowed researchers to identify critical binding determinants and understand the molecular basis of inhibitor potency. Subsequent co-crystal structures with various inhibitor classes revealed recurring interaction patterns, including hydrogen bonding with hinge residues and hydrophobic interactions within adjacent pockets. These findings guided the design of compounds with improved affinity and selectivity.

Crystallographic studies have also enabled researchers to identify structural water molecules that contribute to ligand binding. In many cases, strategically displacing or engaging these water molecules results in improved binding affinity and enhanced selectivity. furthermore, crystal structures have revealed conformational changes induced by inhibitor binding, providing insights into enzyme flexibility and allosteric regulation. Such information is invaluable for the design of inhibitors that exploit unique structural features unavailable in other kinases. As structural databases continue to expand, crystallography remains a cornerstone of GSK-3-focused drug discovery programs.

2.2 MOLECULAR DOCKING AND VIRTUAL SCREENING

Molecular docking has become an essential computational technique for identifying and optimizing GSK-3 inhibitors. Docking algorithms predict the orientation and conformation of small molecules within the target binding site and estimate the strength of protein–ligand interactions. Large virtual libraries containing millions of compounds can be screened rapidly, enabling efficient identification of promising candidates before experimental testing. This approach substantially reduces resource expenditure and increases the probability of discovering novel chemical scaffolds.

In GSK-3 drug discovery, docking studies have identified numerous ATP-competitive and non-competitive inhibitors exhibiting fav interaction profiles. Docking simulations allow researchers to anal hydrogen bonding patterns, hydrophobic contacts, steric complementarity, and electrostatic interactions within the active site.

Compounds demonstrating optimal binding characteristics are prioritized for synthesis and biological evaluation. Additionally, docking supports structure–activity relationship analysis by explaining how specific chemical modifications influence biological activity. Integration of docking with machine learning and artificial intelligence algorithms is further enhancing predictive accuracy and accelerating lead optimization efforts.

2.3 MOLECULARDYNAMICS SIMULATIONS AND PHARMACOPHORE MODEL

Although crystallography and docking provide static snapshots of protein–ligand interactions, proteins are inherently dynamic molecules that undergo continuous conformational changes.Molecular dynamics simulations address this limitation by model atomic movements over time

under physiologically relevant conditions. In GSK-3 inhibitor development, molecular dynamics studies reveal the stability of ligand binding, conformational flexibility of the active site, and the influence of solvent molecules on complex formation.

Such analyses often explain discrepancies between experimental activity and docking predictions, providing deeper insights into the determinants of selectivity and potency.

Pharmacophore model complements these approaches by identifying the essential structural features required for biological activity. Pharmacophore models typically include hydrogen-bond donors, hydrogen-bond acceptors, aromatic rings, hydrophobic groups, and ionizable cent arranged in specific spatial orientations.

These models are used to screen virtual compound libraries and discover new scaffolds possessing the desired pharmacological characteristics. By combining pharmacophore model with molecular dynamics and docking studies, researchers can develop highly refined predictive models that facilitate efficient lead discovery and optimisation

.These models are used to screen virtual compound libraries and discover new scaffolds possessing the desired pharmacological characteristics.

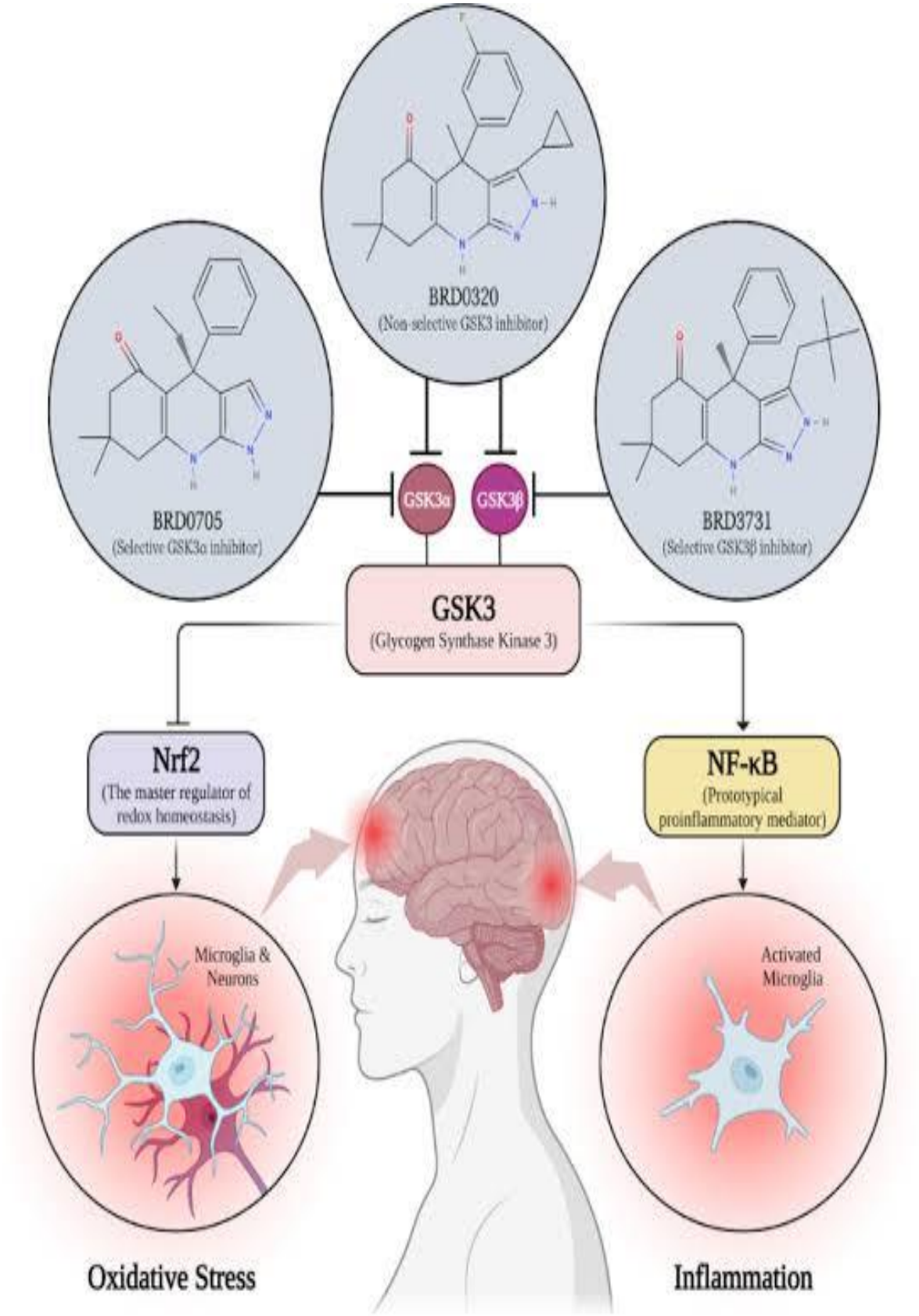
By combining pharmacophore model with molecular dynamics and docking studies, researchers can develop highly refined predictive models that facilitate efficient lead discovery and optimization.These models are used to screen virtual compound libraries and discover new scaffolds possessing the desired pharmacological characteristics.

By combining pharmacophore model with molecular dynamics and docking studies, researchers can develop highly refined predictive models that facilitate efficient lead discovery and optimization.

Pharmacophore models typically include hydrogen-bond donors, hydrogen-bond acceptors, aromatic rings, hydrophobic groups, and ionizable cent arranged in specific spatial orientations.

These models are used to screen virtual compound libraries and discover new scaffolds possessing the desired pharmacological characteristics. By combining pharmacophore model with molecular dynamics and docking studies, researchers can develop highly refined predictive models that facilitate efficient lead discovery and optimisation. Molecular dynamics simulations complement crystallographic and docking studies by capturing protein flexibility and dynamic behaviour. Unlike static structures, molecular dynamics simulations reveal conformational fluctuations occurring over time, providing

insights into ligand stability, binding kinetics, and allosteric communication pathways.. Simulations have demonstrated that GSK-3 undergoes subtle conformational changes influencing inhibitor binding and selectivity. Dynamic analyses help identify transient pockets, flexible loops, and energetically conformations that may serve as targets for novel inhibitors. Free-energy calculations derived.



1. GSK-3 protein–ligand binding structure

GSK-3β kinase ribbon structure

ATP-binding pocket highlighted

inhibitor molecule docked in the active site.

2. Structure-based drug design workflow

GSK-3 crystal structure

↓

Binding pocket analysis

↓

Virtual screening / molecular docking

↓

Lead optimization

↓

Selective GSK-3 inhibitor

3.Selectivity design concept

Compare GSK-3 binding site vs other kinases

Show interactions that improve GSK-3 selectivity:

hydrogen bonds

hydrophobic contacts

unique pocket interactions

4. Medicinal chemistry optimization figure

Lead scaffold → modified anal→ improved potency/select

Disease Association Identified

|

GSK-3 Target Selection

|

Structural Characterization

(X-ray, Cryo-EM, Model)

|

Identification of Binding Sites

├─ ATP Pocket

CONCLUSION

STRUCTURE-BASED APPROACHES IN THE DESIGN OF SELECTIVE GSK-3 INHIBITORS

Glycogen synthase kinase-3 (GSK-3) has emerged as an important therapeutic target because of its central role in multiple cellular processes, including glycogen metabolism, cell differentiation, apoptosis, inflammation, neuronal function, and signal transduction pathways. The two major isoforms, GSK-3α and GSK-3β, participate in diverse biological functions, and their abnormal regulation has been associated with several pathological conditions such as neurodegenerative disorders, diabetes, cancer, mood disorders, and inflammatory diseases. Despite extensive efforts to develop GSK-3 inhibitors, achieving high selectivity remains a major challenge because of the conserved nature of the ATP-binding site among protein kinases. Structure-based drug design (SBDD) has provided a powerful

strategy for overcoming these limitations by enabling rational optimization of molecular interactions, improving potency, selectivity, pharmacokinetic properties, and therapeutic potential.

The availability of high-resolution crystal structures of GSK-3 has significantly accelerated the development of selective inhibitors. Structural information has allowed researchers to important regions of the enzyme, including the ATP-binding pocket, hinge region, activation loop, substrate recognition sites, and allosteric binding regions. Traditional kinase inhibitors frequently target the ATP-binding site; however, this approach often results in poor selectivity because ATP-binding domains are highly conserved across kinases.

Structure-based approaches have therefore focused on identifying unique structural features within GSK-3 that can be exploited for selective inhibition. Detailed structural analysis has revealed subtle differences in pocket shape, amino acid composition, and conformational flexibility that can be utilized to design inhibitors with improved specificity.

One of the major achievements of structure-based design has been the development of ATP-competitive inhibitors with enhanced selectivity profiles. Through molecular docking, molecular dynamics simulations, and structure–activity relationship studies, researchers have been able to identify chemical scaffolds capable of forming strong interactions with critical residues in the GSK-3 binding pocket. Interactions with hinge residues, particularly hydrogen bonding networks, contribute significantly to inhibitor affinity.

Additional interactions with unique residues surrounding the ATP pocket provide opportunities to distinguish GSK-3 from other kinases. Optimization of these interactions has resulted in several classes of selective GSK-3 inhibitors, including heterocyclic compounds, aminopyrimidines, pyrazines, thiazoles, and other small-molecule scaffolds.

The structure-guided optimization of inhibitors has also emphasized the importance of achieving isoform selectivity between GSK-3α and GSK-3β. Although these isoforms share considerable sequence similarity, structural differences in specific regions offer opportunities for selective targeting. GSK-3β has historically received greater attention because of its involvement in tau phosphorylation and neuronal disorders, whereas GSK-3α has been linked to metabolic regulation and other signal pathways.

Designing isoform-selective inhibitors remains challenging, but advances in structural biology and computational chemistry have improved understanding of isoform-specific conformational states and binding interactions. Future structure-based strategies may allow the development of inhibitors that selectively modulate individual isoforms, reducing unwanted biological effects.

Allosteric inhibition represents another promising direction in GSK-3 inhibitor discovery. Unlike ATP-site inhibitors, allosteric inhibitors bind to less conserved regions of the enzyme, providing greater opportunities for selectivity. Structural studies have identified alternative binding pockets that can regulate enzyme activity through conformational changes. Targeting these regions may avoid many limitations associated with ATP competition and reduce off-target kinase inhibition. The development of allosteric GSK-3 inhibitors demonstrates how structural information can expand the range of possible therapeutic strategies beyond conventional kinase inhibition.

Another challenge is improving drug-like properties of GSK-3 inhibitors. Many potent inhibitors identified through structure-based screening may suffer from poor solubility, limited bioavailability, metabolic instability, or toxicity. Structural optimization must therefore balance target affinity with pharmacokinetic and safety characteristics. The incorporation of medicinal chemistry principles, including optimization of molecular size, polarity, flexibility, and metabolic stability, is essential for converting promising inhibitors into clinically useful candidates.

The application of structural biology has also contributed to understanding inhibitor-induced conformational changes in GSK-3. Many kinases exist in multiple conformational states, and inhibitors may stabilize inactive or active-like forms. Recognizing these conformational preferences provides additional opportunities for selective inhibitor development. Future studies combining cryo-electron microscopy, advanced crystallography, and computational simulations may reveal new regulatory states of GSK-3 and uncover previously unknown drug-binding sites.

In conclusion, selective GSK-3 inhibitor development represents an excellent example of how structural knowledge can guide modern drug discovery. While challenges related to isoform specificity, safety, and clinical translation remain, structure-based design provides a strong foundation The combination of innovative computational methods and experimental structural approaches will continue to expand the possibilities for designing next-generation GSK-3 inhibitors with improved therapeutic outcomes.

REFERENCES

1. Patel DS, Dessalew N, Iqbal P, Bharatam PV.Structure-Based Approaches in the Design of GSK-3 Selective Inhibitors.Current Protein & Peptide Science. 2007;8(4):352–364.DOI: 10.2174/138920307781369409

2.Bertrand JA, Thieffine S, Vulpetti A, et al.Structural Characterization of the GSK-3β Active Site Using Selective and Non-selective ATP-mimetic Inhibitors.Journal of Molecular Biology. 2003;333:393–407.

3.Vulpetti A, Crivori P, Cameron A, et al.Structure-Based Approaches to Improve Selectivity: CDK2–GSK3β Binding Site Analysis.

Journal of Chemical Information and Modeling. 2005;45:1282–1290.

4.Lo Monte F, Kramer T, Gu J, et al.Structure-based optimization of oxadiazole-based GSK-3 inhibitors.European Journal of Medicinal Chemistry. 2013;61:26–40.

[6:33 pm, 18/06/2026] +91 94946 55637: 5.Ombrato R, Cazzolla N, Mancini F, et al.

Structure-Based Discovery of 1H-Indazole-3-carboxamides as a Novel Structural Class of Human GSK-3 Inhibitors.

Journal of Chemical Information and Modeling. 2015;55:2540–2551

6. Davies MP, Benitez R, Perez C, et al.Structure-Based Design of Potent Selective Nanomolar Type-II Inhibitors of Glycogen Synthase Kinase-3β.Journal of Medicinal Chemistry. 2021;64:1497–1509.

7. Amaral B, Capacci A, Anderson T, et al.Elucidation of the GSK3α Structure Informs the Design of Novel, Paralog-Selective Inhibitors.ACS Chemical Neuroscience. 2023;14:1080–1094.

8. Dajani R, et al. Crystal structure of glycogen synthase kinase 3 beta. Cell. 2001;105(6):721-32. PMID: 11440715

9.Eldar-Finkelman H, Martinez A. GSK-3 inhibitors: preclinical and clinical focus on CNS. Front Mol Neurosci. 2011;4:32. PMID: 22065134

10. Wagner FF, et al. Inhibitor binding to an allosteric site of GSK-3β. Nat Chem Biol. 2018;14(10):964-972. PMID: 30127372

11. Manoukian AS, Woodgett JR. Role of GSK-3 in cell signaling. Adv Cancer Res. 2002;84:179–221.

12. Jope RS, Johnson GVW. The glamour and gloom of GSK-3. Trends Biochem Sci. 2004;29:95–102.

13. Arfeen M, Bharatam PV. Design of Glycogen Synthase Kinase-3 Inhibitors: Recent Advancements. Curr Pharm Des. 2013;19:260–276.

14. Xu M, Wang SL, Zhu L, et al. SAR studies of synthetic GSK-3β inhibitors: a critical review. Eur J Med Chem. 2019;164:448–470.

15. Duchowicz PR, Castro EA. QSAR studies for pharmacological inhibition of GSK-3. Med Chem. 2007;3:393–417.

16. Martinez A, Alonso M, Castro A, et al. First non-ATP competitive GSK-3 inhibitors. J Med Chem. 2002.

17. Martinez A, Castro A. GSK-3 inhibitors and therapeutic applications. Med Res Rev. 2005.

18. Meijer L, Skaltsounis AL, Magiatis P, et al. GSK-3 selective inhibitor indirubin derivatives. Chem Biol. 2003.

19. Polychronopoulos P, Magiatis P, Skaltsounis AL, et al. Structural basis of indirubin GSK-3 inhibition. J Med Chem. 2004.

20. Leclerc S, Garnier M, Hoessel R, et al. Indirubins inhibit GSK-3 and CDKs. J Biol Chem. 2001.

21. Hoessel R, Leclerc S, Endicott JA, et al. Indirubin derivatives as protein kinase inhibitors. Nat Cell Biol. 1999.

22. Bertrand JA, Vulpetti A, Leclerc S, et al. Structural studies of paullones bound to GSK-3β. J Med Chem. 2005.

23. Kunick C, Lauenroth K, Wieking K, et al. Paullones as GSK-3 inhibitors. Bioorg Med Chem Lett. 2004.

24. Leost M, Schultz C, Link A, et al. Paullones inhibit cyclin-dependent kinases and GSK-3. Eur J Biochem. 2000.

25. Meijer L. Chemical inhibitors of GSK-3. Prog Cell Cycle Res. 2003.

26. Cohen P, Frame S. The renaissance of GSK-3. Nat Rev Mol Cell Biol. 2001.

27. Bain J, McLauchlan H, Elliott M, Cohen P. Comparison of GSK-3 inhibitor selectivity. Biochem J. 2003.

28. Bain J, Plater L, Elliott M, et al. The selectivity of protein kinase inhibitors. Biochem J. 2007.

29. Zhang HC, White KB, Ye H, et al. A structure-guided approach to GSK-3 inhibitors. Bioorg Med Chem Lett. 2004.

30. Wagman AS, Johnson KW, Bussiere DE. Discovery of GSK-3 inhibitors. Curr Pharm Des. 2004.

31. Bhat RV, Shanley J, Correll MP, et al. Regulation of GSK-3 by small molecules. J Biol Chem. 2000.

32. Coghlan MP, Culbert AA, Cross DAE, et al. Selective small molecule inhibitor of GSK-3. Chem Biol. 2000.

33. Culbert AA, Brown MJ, Frame S, et al. GSK-3 inhibitor CHIR99021. J Biol Chem. 2001.

34. Ring DB, Johnson KW, Henriksen EJ, et al. Selective GSK-3 inhibitor. Diabetes. 2003.

35. Eldar-Finkelman H, Martinez A. GSK-3 inhibitors: therapeutic prospects. Future Med Chem. 2011.

36. Sutherland C. GSK-3 inhibitors as therapeutic agents. Front Mol Neurosci. 2011.

37. Zhou W, Doble B, Pantazopoulou M, et al. Novel GSK-3 inhibitors. Mol Cell Biochem. 2008.

38. Sherry DM, Stewart M, Cumming SA, et al. Structure-guided GSK-3 inhibitor design. J Med Chem. 2005.

39. Eldar-Finkelman H, Eisenstein M. Peptide and small molecule inhibitors of GSK-3. Trends Pharmacol Sci. 2009.

40. Martinez A, Gil C, Perez DI. GSK-3 inhibitors in Alzheimer's disease. Med Res Rev. 2011.

41. Medina M, Wandosell F. Deconstructing GSK-3 inhibitors. Front Mol Neurosci. 2011.

42. Pandey MK, DeGrado TR. GSK-3 inhibitors and imaging. Theranostics. 2016.

43. Beaulieu JM, Gainetdinov RR. The physiology of GSK-3. Pharmacol Rev. 2011.

44. Cohen P, Goedert M. GSK-3 inhibitors in neurodegeneration. Nat Rev Drug Discov. 2004

45. Palomo V, Perez DI, Gil C, Martinez A. Multi-target GSK-3 inhibitors. Chem Soc Rev. 2011.

46. Medina M, Avila J. GSK-3 and Alzheimer disease. Int J Alzheimer Dis. 2010.

47. Llorens-Martin M, Jurado J, Hernandez F, Avila J. GSK-3 inhibitors and tau pathology. CNS Neurol Disord Drug Targets. 2014.

48. Medina M, Avila J. GSK-3 and Alzheimer disease. Int J Alzheimer Dis. 2010.

49. Ramurthy S, Pfister KB, Boyce RS, et al. Discovery and optimization of novel pyridines as selective GSK-3 inhibitors. Bioorg Med Chem Lett. 2020.

50. Ombrato R, Cazzolla N, Mancini F, et al. Structure-based discovery of indazole carboxamides as GSK-3 inhibitors. J Chem Inf Model. 2015.

51. Lo Monte F, Kramer T, Gu J, et al. Structure-based optimization of oxadiazole GSK-3 inhibitors. Eur J Med Chem. 2013.

52. Wang Y, Zhang Y, et al. Virtual screening and docking studies of GSK-3 inhibitors. J Chem Inf Model.

53. Chen P, Guo Y, et al. Molecular docking based discovery of GSK-3β inhibitors. Bioorg Chem.

54. Dasgupta A, Kalidass K, et al. Identification of brain penetrant GSK-3β inhibitors by docking and MD simulation. J Biomol Struct Dyn. 2025.

55. Amaral B, Capacci A, Anderson T, et al. Elucidation of GSK-3α structure for paralog selective inhibitors. ACS Chem Neurosci. 2023