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Mini-Review

Potent GSK-3β Inhibition: Exploring Emerging Chemical Scaffolds and Biological Activities.

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ABSTRACT

This mini-review embarks on a deep dive into the exciting world of glycogen synthase kinase-3 beta (GSK-3β) inhibition, a burgeoning field with immense potential for combatting a diverse range of diseases. GSK-3β, a versatile serine/threonine kinase, acts as a pivotal regulator in intricate pathways governing key physiological and pathological processes. Its fingerprints are found in neurodegenerative disorders like Alzheimer's and Parkinson's, the complexities of cancer progression, the metabolic imbalances seen in diabetes, and the inflammatory storm characteristic of autoimmune diseases. Unveiling new opportunities for GSK-3β modulation lies in the exploration of novel chemical scaffolds, venturing beyond the confines of traditional structures. This review meticulously details recent advancements in the identification and optimization of small molecules, showcasing innovative chemical frameworks as promising GSK-3β inhibitors. By venturing out of the familiar, researchers are unlocking a treasure trove of possibilities, each with unique biological activities waiting to be explored. Delving deeper, the review sheds light on the diverse biological consequences of GSK-3β inhibition, painting a vibrant picture of the potential therapeutic applications across

various disease landscapes. From neuroprotective effects that offer hope in neurodegenerative disorders to the potential for modulating tumor growth and inflammation, the possibilities seem endless.

Keywords: GSK-3β, Cancer, Serine Threonine

1-Introduction

Glycogen synthase kinase-3 is a member of the cyclin-dependent kinase (CDK) family of proline-directed kinases, which also includes cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), GSKs, and CDK-like kinases (CLKs)[1]. It is found in two isoforms, GSK-3α and 3β, which are both highly conserved kinases that encode 51 and 47 kDa proteins, respectively [2]. With a β-strand domain (residues 25–138) at the N-terminal end and an α-helical domain (residues 139–343) at the C-terminal end, GSK-3β possesses the conventional two-domain kinase fold. Situated near the meeting point of the β-strand and α-helical domains, the hinge and glycine-rich loop encircle the ATP-binding site. The substrate binding groove's surface is occupied by the activation loop, which is made up of residues 200–226. Outside the core kinase fold, the C-terminal 39 residues (residues 344–382) create a tiny domain that presses up against the α-helical domain. There are seven antiparallel β-strands that make up the β-strand domain. The β-barrel formed by strands 2–6 is broken up between strands 4 and 5 by a short helix (residue 96–102) that packs against the β-barrel. All kinases share this helix, and two of its residues are essential to the enzyme's catalytic activity. The alignment of the two domains involves Arg 96. Lys 85 is an essential residue in catalysis, and Glu 97 is positioned at the active site where it forms a salt bridge with it[3].GSK-3α and 3β are generated from two different GSK-3 genes[4]. Both isomers found in the cell and tissues and they are close to each other in physiological activity [5]. GSK-3β is the most dominant isoform. So, the GSK-3β has been associated with a lot of human disease including cancer, that why it possesses strong therapeutic activity as anticancer agent [6]. Recent studies reported GSK-3β as strong target in different types of cancer there for it is expressed in the nucleus of the cancer cells [7]. So GSK-3β inhibitors play an important role in apoptosis and proliferation of the cell cycle so it has tumor suppressor action in different malignant tumors such as skin, breast, oral and lung and so on [8]. Different chemical inhibitors of synthetic and natural source have reported as GSK-3β inhibitors containing pyrimidine, purines, or pyrimidin-4-one moieties or other bioisosteres ring [9]. GSk-

3β activity regulated by extracellular signals that typically induce a rapid and reversible response[10].GSK-3β is a crucial enzyme involved in various cellular processes, including glycogen metabolism, cell cycle regulation, and neuronal development[11].

Dysregulation of GSK-3β has been implicated in several diseases, including neurodegenerative disorders and cancer[12]. GSK is dual specificity kinase differentially regulated by a variety of complex mechanisms that control its activity and each dependent upon specific signaling pathway that regulatory mechanism can be classified as the following AKT, IKL, PKA and P90 RSK and many physiological situations of inhibition of GSK-3 correlated with serine phosphorylation such as insulin /IGF1, NGF or estradiol treatment, not only in neurons. and also used in treatment of cancer[13]. Wnt/ β-catenin signaling pathway family of secreted, cysteine-rich, and glycosylated protein ligands. Wnt signal transduction ultimately results in the activation of genes regulated by the T-cell factor (TCF)/lymphoid enhancer factor (LEF) family of transcription factors and is implicated in tumorigenesis and malignancy. In the absence of Wnt signals, free cytoplasmic β-catenin is incorporated into a cytoplasmic complex that includes Axin, GSK3β and adenomatous polyposis coli (APC)[14]. This enables GSK-3β to phosphorylate β-catenin and results in degradation of β-catenin. Wnt signaling inactivates GSK-3β and prevents it from phosphorylating [15].β-catenin, thus stabilizing β-catenin in the cytoplasm[16].

In addition to β-catenin, many proto-oncogenic or tumor suppressing transcription and translation factors are substrates of GSK-3β [17]. For example, tumor suppressor transcription factor p53 is a target of GSK-3β. GSK-3β regulates the levels as well as intracellular localization of p53. GSK-3β forms a complex with nuclear p53 to promote p53-induced apoptosis. GSK-3β directly modulates the activity of transcription factors, activator protein1 (AP-1) and nuclear factor- κB (NF- κB) [18]. Both transcription factors play a critical role in neoplastic transformation and tumor development. Various chemical scaffolds including Indole, pyrrolopyrimidine ,Pyrazine ring, Thiazole ,Furopyrimidine, Pyrido isoindolone and Quinolone ,demonstrated promising biological activity as GSK-3β inhibitors, offering potential therapeutic avenues for a range of diseases[19].

Here, we explore some notable chemical scaffolds that have shown efficacy in inhibiting GSK-3β.

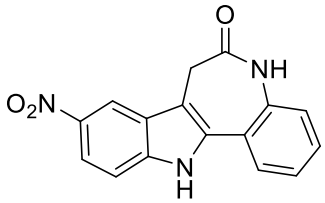
2-Different scaffolds of GSK-3 inhibitors

2.1. Indole derivatives

A small-molecule inhibitor called alsterpaullone targets cyclin-dependent kinases (CDK), causing cell cycle arrest and encouraging tumour cell death, it has been discovered that the drug's ability to induce apoptosis in cancer is mediated via the mitogen-activated protein kinase (MAPK) signalling pathway. Alsterpaullone targets relevant human protein kinases associated with Alzheimer dementia (AD), even though its focus is on anti-cancer treatment. Numerous protein kinases have been discovered to phosphorylate tau in vitro, which aids in the development of AD. Among the physiologically significant proteins, GSK-3β seems to be one of alsterpaullone's targets.

High amounts of GSK-3 are widely expressed in the brain and have been linked to axonal expansion, neuronal polarization, and the Wnt signaling pathway, among other neuronal activities. Dysregulation of GSK-3β, an isozyme of GSK-3, results in a variety of fatal illnesses, including neurodegenerative conditions like Alzheimer's disease. Granulovacuolar degeneration neurons have highly active GSK-3β, which hyperphosphorylated tau proteins linked with microtubules, causing neurofibrillary tangles to accumulate fatally and impair neuronal connections. However, GSK-3β also causes neurotoxicity by mediating the synthesis of Aβ from the precursor proteins. It has been observed that a variety of GSK-3 inhibitors decrease tau hyperphosphorylation and the quantity of Aβ in both neuronal and nonneuronal cells. More significantly, it was demonstrated that these inhibitors effectively promoted nerve cell proliferation, migration, differentiation, and hippocampus neurogenesis.

This illustrates why the enzyme should be viewed as a target for AD therapy, and alsterpaullone, as an ATP competitive inhibitor, work to inhibit GSK-3β activation[20]. Alsterpaullone is an inhibitor of cyclin-dependent kinase (CDK), which is thought to be a treatment for group 3 medulloblastomas. It modulates the progression of the cell cycle. Alsterpaullone is also a strong GSK-3 inhibitor, with IC_{50} values of 4nM for both GSK-3α and 3β. It has been shown to induce apoptosis and promote loss in clonogenicity in the Jurkat cell line Alsterpaullone exhibits anticancer action and shows promise in the research of proliferative and neurological illnesses, induces apoptosis in leukemia cell line[21, 22].

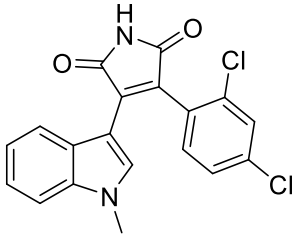


(1) Alsterpaullone
IC_{50} of GSK-3β= 4nM

SB216763 is a strong and selective GSK-3 cell-permeable inhibitor, equally efficient in inhibiting human GSK-3α and 3β at an IC_{50} of 34.3 nM. It is a maleimide derivative have the highly selective nanomolar GSK-3 inhibitor arylindole maleimide was created by GlaxoSmithKline and has demonstrated neuroprotective effects against a range of pro-apoptotic conditions, such as trophic deprivation, Aβ toxicity, heat shock, ethanol, NMDA excitotoxicity, and polyglutamine toxicity due to the HD protein.

It's interesting to note that reduced Aβ neurotoxic effects, such as τ phosphorylation, caspase-3, and the activity of stress-activated kinase JNK (c-Jun N-terminal kinase), were observed in an AD model of mice injected with Aβ peptide. But in healthy mice, the same inhibitor caused abnormalities in behavior and neurodegenerative-like consequences, indicating that over-inhibition of GSK-3 may lead to situations that impair normal neuronal function.

SB216763 competes with ATP and effectively suppresses the GSK-3α and 3β isozymes activities functions as a neuroprotectant and stops the PI3-kinase pathway's induction of neuronal cell death, Additionally avoids myocardial ischemia, slows preconditioning, and reduces infarct size[23, 24].



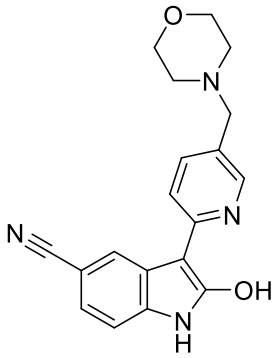
(2) SB216763
IC_{50} of GSK-3β = 34.3 nM

AZD1080 has a IC_{50} of 6.9 nM and 31 nM for GSK-3α and 3β, respectively. This means that it is more selective for GSK-3α, but it is still a potent inhibitor of both isoforms. By

inhibiting GSK-3, AZD1080 has the potential to treat a wide range of diseases. For example, Clinical trials for cancer, Parkinson's disease, and Alzheimer's disease are presently being conducted on it.

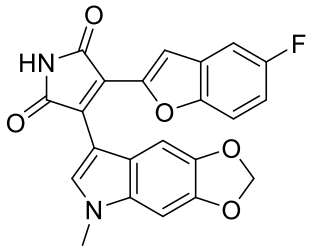
Apart from its potency and selectivity, AZD1080 also has the benefit of being able to be taken orally and having brain penetration.

This means that It is a potentially effective medication for the treatment of neurological illnesses because it may be administered as a pill and crosses the blood-brain barrier[25, 26].



(3) AZD1080
IC_{50} of GSK-3β = 31 nM

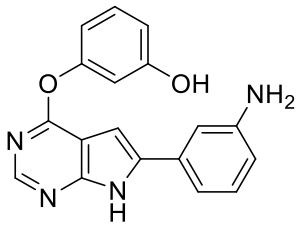
9-ING-41 is a potent GSK-3 inhibitor that has been shown to inhibit both GSK-3α and 3β with IC_{50} values of 710 nM, respectively. It has been shown to have in vivo and in vitro anticancer activities. 9-ING-41 has also been shown to have activity against multiple myeloma cells[27].



(4) 9-ING-41
IC_{50} of GSK-3β = 710 nM

2.2. Pyrrolopyrimidine derivative

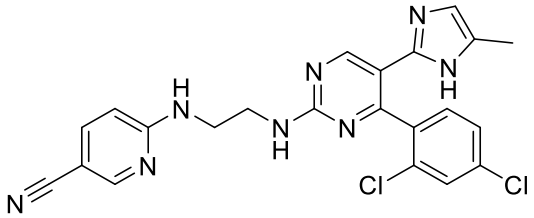
TWS119 is a specific inhibitor of (GSK-3β) with an IC_{50} of 30 nM. It activates the Wnt/β-catenin pathway. TWS119 acts as a Wnt pathway activator since GSK-3 is a serine/threonine kinase that is a crucial inhibitor of the Wnt pathway induces neuronal differentiation in P19 EC cells and primary mouse ESCs, It has been shown to facilitate long-term neurological recovery via modulating microglia polarization after experimental stroke[28, 29].



(5) TWS119
IC_{50} of GSK-3β = 30 nM

2.3. Pyrazine derivatives

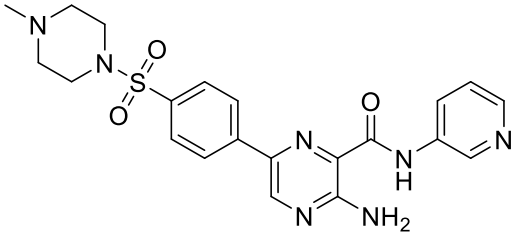
CHIR-99021 is an extremely potent that inhibits GSK-3β (IC_{50} = 0.003 nM) as well as GSK-3α (IC_{50} = 0.002 nM). Amino pyrazine derivative that acts as an inhibitor of the enzyme GSK-3. CHIR99021 functions as a Wnt activator[30].



(6) CHIR-99021
IC_{50} of GSK-3β= 0.003 nM

AZD2858 has a dual inhibitor of GSK-3α and 3β isoforms, with The IC_{50} values of GSK-3 inhibitors for GSK-3α and 3β are 0.9 and 5 nM, respectively. It activates Wnt signaling and increases bone mass in rats. AZD2858 is The IC_{50} values of GSK-3 inhibitors for GSK-3α and 3β are 0.9 and 5 nM, respectively. AZD2858 has a significant contribution to fracture repair.

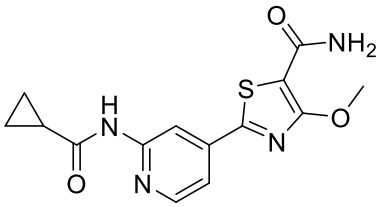
Without a noticeable endochondral component, the fractures healed with a bony callus, indicating that AZD2858 pushes mesenchymal cells onto the osteoblastic route[31, 32].



(7) AZD2858
IC_{50} of GSK-3β = 5 Nm

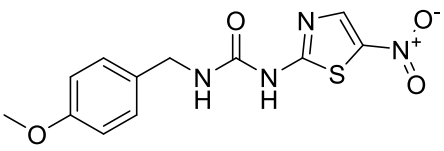
2.4. Thiazole derivatives

2-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-methoxythiazole-5-carboxamide is a GSK-3β inhibitor particularly effective against GSK-3, preventing hyperphosphorylated tau (pTau) protein from reaching elevated levels, which is thought to be the cause of the formation of neurofibrillary tangles, one of the clinical hallmarks in the brains of Alzheimer's patients. IC_{50}=1100nM[33, 34].



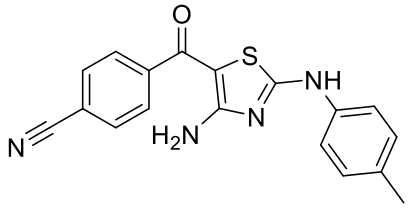
(8) IC_{50} of GSK-3β = 1100nM

AR-A01448 is a GSK-3β inhibitor that has been shown to inhibit GSK-3β activity *in vitro* with IC_{50} =104nM the central core consists of a urea moiety, which is a common building block in many pharmaceuticals and other organic compounds. Attached to the urea are two aromatic rings: a pyridine ring and a fluorinated quinoline ring. Additionally, a dihydropyran ring is linked to the pyridine ring [35].



(9) IC_{50} of GSK-3β = 104nM

ABC-1183 has chemical name 4-(4-amino-2-(*p*-tolylamino)thiazole-5-carbonyl)benzonitrile is an oral diaminothiazole molecule that is being developed by Apogee Biotechnology for the control of inflammation and cancer. It is also an orally active selective dual GSK-3 and CDK9 inhibitor. ABC1183 has IC_{50} values of 657 nM, 327 nM, and 321 nM GSK-3α , 3β, and CDK9/cyclin T1 inhibition, respectively. It possesses anti-tumor and anti-inflammatory properties. [36].

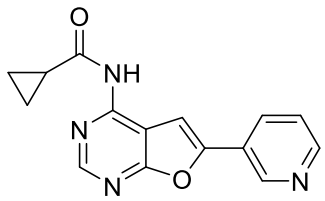


ABC-1183

(10) IC_{50} of GSK-3β = 657 nM

2.5. Furopyrimidine derivative

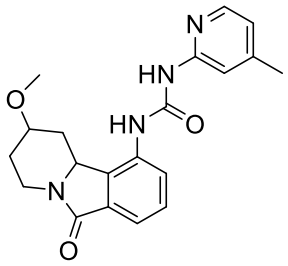
N-(6-(pyridin-3-yl)furo[2,3-*d*]pyrimidin-4-yl)cyclopropanecarboxamide is an inhibitor of GSK-3β. Serine/threonine protein kinase GSK-3β is essential for more than one set of biological functions, including cell development, death, and glycogen metabolism[37].



(11) IC_{50} of GSK-3β = 5 nM

2.6. Pyrido isoindolone derivative

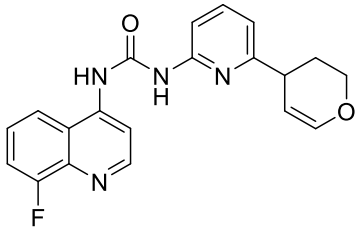
1-(2-methoxy-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-10-yl)-3-(4-methylpyridin-2-yl)urea This was one of those compounds designed to alter the tetrahydro (pyridine isoindolone) (valmerin) skeleton's structure, demonstrating anticancer action against cell lines. it is showing IC_{50} against CDK5=320nM, GSK-3α and 3β =32nM, CDK5/GSK-3 =10000nM, DYRK1A= >10000nM[38].



(12) IC_{50} of GSK-3β = 32nM

2.7. Quinolone derivative

1-(6-(3,4-dihydro-*2H*-pyran-4-yl)pyridin-2-yl)-3-(8-fluoroquinolin-4-yl)urea is a molecule with a complex structure containing several functional groups. These various functional groups likely contribute to the molecule's unique properties and potential biological activities, showing IC_{50}=<100nM against GSK-3β[39].



(13) IC_{50} of GSK-3β =<100nM

3. Conclusion

In conclusion, the last five years have witnessed significant progress in the field of GSK-3β inhibition, with the identification of novel chemical scaffolds and their therapeutic implications. The exploration of these compounds in various disease contexts opens exciting possibilities for the development of targeted and effective treatments. Researchers continue to unravel the complexities of GSK-3β signaling, providing a foundation for future breakthroughs in drug discovery and personalized medicine.

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- **Conflict of Interest**

There is no competing of interest.

Author contribution: K.A.M.A. created the entire study, supervised the articles, this article was written by J.S.S. All of the authors reviewed the article.

4. References

1. Gwack Y, Sharma S, Nardone J, Tanasa B, Iuga A, Srikanth S, Okamura H, Bolton D, Feske S, Hogan PG: **A genome-wide Drosophila RNAi screen identifies DYRK-family kinases as regulators of NFAT**. *Nature* 2006, **441**(7093):646-650.
2. Cormier KW, Larsen B, Gingras A-C, Woodgett JR: **Interactomes of Glycogen Synthase Kinase-3 Isoforms**. *Journal of Proteome Research* 2023, **22**(3):977-989.
3. ter Haar E, Coll JT, Austen DA, Hsiao H-M, Swenson L, Jain J: **Structure of GSK3β reveals a primed phosphorylation mechanism**. *Nature structural biology* 2001, **8**(7):593-596.
4. Doble BW, Patel S, Wood GA, Kockeritz LK, Woodgett JR: **Functional redundancy of GSK-3α and GSK-3β in Wnt/β-catenin signaling shown by using an allelic series of embryonic stem cell lines**. *Developmental cell* 2007, **12**(6):957-971.
5. van der Kolk MR, Janssen MA, Rutjes FP, Blanco-Ania D: **Cyclobutanes in small-molecule drug candidates**. *ChemMedChem* 2022, **17**(9):e202200020.
6. Das A, Bhattacharya B, Roy S: **Decrypting a path based approach for identifying the interplay between PI3K and GSK3 signaling cascade from the perspective of cancer**. *Genes & Diseases* 2022, **9**(4):868-888.
7. Walz A, Ugolkov A, Chandra S, Kozikowski A, Carneiro BA, O'Halloran TV, Giles FJ, Billadeau DD, Mazar AP: **Molecular pathways: revisiting glycogen synthase kinase-3β as a target for the treatment of cancer**. *Clinical Cancer Research* 2017, **23**(8):1891-1897.
8. Zhao H, Ming T, Tang S, Ren S, Yang H, Liu M, Tao Q, Xu H: **Wnt signaling in colorectal cancer: Pathogenic role and therapeutic target**. *Molecular cancer* 2022, **21**(1):144.
9. Khan I, Tantray MA, Hamid H, Alam MS, Sharma K, Kesharwani P: **Design, synthesis, in vitro antiproliferative evaluation and GSK-3β kinase inhibition of a new series of pyrimidin-4-one based amide conjugates**. *Bioorganic Chemistry* 2022, **119**:105512.
10. Medina M, Wandosell F: **Deconstructing GSK-3: the fine regulation of its activity**. *International journal of Alzheimer's disease* 2011, **2011**.
11. Yu H, Xiong M, Zhang Z: **The role of glycogen synthase kinase 3 beta in neurodegenerative diseases**. *Frontiers in Molecular Neuroscience* 2023, **16**.
12. Lai S, Wang P, Gong J, Zhang S: **New insights into the role of GSK-3β in the brain: from neurodegenerative disease to tumorigenesis**. *PeerJ* 2023, **11**:e16635.
13. Vilimek DAH: **Cytokine regulation of glycogen synthase kinase-3 (GSK-3)**. University of British Columbia; 2001.

14. MacDonald BT, Tamai K, He X: **Wnt/β-catenin signaling: components, mechanisms, and diseases**. *Developmental cell* 2009, **17**(1):9-26.
15. Zhan L, Liu D, Wen H, Hu J, Pang T, Sun W, Xu E: **Hypoxic postconditioning activates the Wnt/β-catenin pathway and protects against transient global cerebral ischemia through Dkk1 Inhibition and GSK-3β inactivation**. *The FASEB Journal* 2019, **33**(8):9291-9307.
16. Behrens J: **Control of β-catenin signaling in tumor development**. *Annals of the New York Academy of Sciences* 2000, **910**(1):21-35.
17. Sun Y, Guo F, Bagnoli M, Xue F-X, Sun B-C, Shmulevich I, Mezzanzanica D, Chen K-X, Sood AK, Yang D: **Key nodes of a microRNA network associated with the integrated mesenchymal subtype of high-grade serous ovarian cancer**. *Chinese journal of cancer* 2015, **34**(1):28-40.
18. Thotala DK, Hallahan DE, Yazlovitskaya EM: **Glycogen synthase kinase 3β inhibitors protect hippocampal neurons from radiation-induced apoptosis by regulating MDM2-p53 pathway**. *Cell Death & Differentiation* 2012, **19**(3):387-396.
19. Li Z, Yin B, Zhang S, Lan Z, Zhang L: **Targeting protein kinases for the treatment of Alzheimer's disease: recent progress and future perspectives**. *European Journal of Medicinal Chemistry* 2023:115817.
20. Xu Y, Kong J, Hu P: **Computational drug repurposing for Alzheimer's disease using risk genes from GWAS and single-cell RNA sequencing studies**. *Frontiers in Pharmacology* 2021, **12**:617537.
21. Tolle N, Kunick C: **Paullones as inhibitors of protein kinases**. *Current Topics in Medicinal Chemistry* 2011, **11**(11):1320-1332.
22. Arafa RK, Elghazawy NH: **Personalized Medicine and Resurrected Hopes for the Management of Alzheimer's Disease: A Modular Approach Based on GSK-3 β Inhibitors**. *Personalised Medicine: Lessons from Neurodegeneration to Cancer* 2017:199-224.
23. Wang W, Yang Y, Xiong Z, Kong J, Fu X, Shen F, Huang Z: **Inhibition of glycogen synthase kinase 3beta ameliorates triptolide-induced acute cardiac injury by desensitizing mitochondrial permeability transition**. *Toxicology and applied pharmacology* 2016, **313**:195-203.
24. Demuro S, Di Martino RM, Ortega JA, Cavalli A: **GSK-3β, FYN, and DYRK1A: master regulators in neurodegenerative pathways**. *International Journal of Molecular Sciences* 2021, **22**(16):9098.
25. McCubrey JA, Steelman LS, Bertrand FE, Davis NM, Sokolosky M, Abrams SL, Montalto G, D'Assoro AB, Libra M, Nicoletti F: **GSK-3 as potential target for therapeutic intervention in cancer**. *Oncotarget* 2014, **5**(10):2881.
26. Khan SS, Janrao S, Srivastava S, Singh SB, Vora L, Khatri DK: **GSK-3β: An exuberating neuroinflammatory mediator in Parkinson's disease**. *Biochemical Pharmacology* 2023:115496.
27. Karati D, Shaoo KK, Mahadik K, Kumr D: **Glycogen synthase kinase-3β inhibitors as a novel promising target in the treatment of cancer: Medicinal chemistry perspective**. *Results in Chemistry* 2022, **4**:100532.
28. Davies SG, Kennewell PD, Russell AJ, Seden PT, Westwood R, Wynne GM: **Stemistry: the control of stem cells in situ using chemistry**. *Journal of Medicinal Chemistry* 2015, **58**(7):2863-2894.

29. Dash AK, Mukherjee D: **An Overview on Diversity Oriented Synthesis, Such as an Enormous Implications for the Discovery of Small Molecules**.
30. Wagner FF, Bishop JA, Gale JP, Shi X, Walk M, Ketterman J, Patnaik D, Barker D, Walpita D, Campbell AJ: **Inhibitors of glycogen synthase kinase 3 with exquisite kinome-wide selectivity and their functional effects**. *ACS Chemical Biology* 2016, **11**(7):1952-1963.
31. Silva-García O, Cortés-Vieyra R, Mendoza-Ambrosio FN, Ramírez-Galicia G, Baizabal-Aguirre VM: **GSK3α: an important paralog in neurodegenerative disorders and cancer**. *Biomolecules* 2020, **10**(12):1683.
32. Gilmour PS, O'Shea PJ, Fagura M, Pilling JE, Sanganee H, Wada H, Courtney PF, Kavanagh S, Hall PA, Escott KJ: **Human stem cell osteoblastogenesis mediated by novel glycogen synthase kinase 3 inhibitors induces bone formation and a unique bone turnover biomarker profile in rats**. *Toxicology and applied pharmacology* 2013, **272**(2):399-407.
33. Yadav MR, Barmade MA, Chikhale RV, Murumkar PR: **Computational Modelling of Kinase Inhibitors as Anti-Alzheimer Agents**. *Computational Modeling of Drugs Against Alzheimer's Disease* 2018:347-417.
34. Sivaprakasam P, Han X, Civiello RL, Jacutin-Porte S, Kish K, Pokross M, Lewis HA, Ahmed N, Szapiel N, Newitt JA: **Discovery of new acylaminopyridines as GSK-3 inhibitors by a structure guided in-depth exploration of chemical space around a pyrrolopyridinone core**. *Bioorganic & medicinal chemistry letters* 2015, **25**(9):1856-1863.
35. Liang D, Wang Y, Yan T, Wang Z: **Synthesis of deuterium-labeled 1-(4-methoxybenzyl)-3-(5-nitrothiazol-2-yl) urea (AR-A014418) as an internal standard for LC–MS analysis**. *Journal of Radioanalytical and Nuclear Chemistry* 2020, **325**:217-222.
36. Schrecengost RS, Green CL, Zhuang Y, Keller SN, Smith RA, Maines LW, Smith CD: **In vitro and in vivo antitumor and anti-inflammatory capabilities of the novel GSK3 and CDK9 inhibitor ABC1183**. *Journal of Pharmacology and Experimental Therapeutics* 2018, **365**(1):107-116.
37. Xu M, Wang S, Zhu L, Wu P, Dai W, Rakesh K: **Structure-activity relationship (SAR) studies of synthetic glycogen synthase kinase-3β inhibitors: a critical review**. *European journal of medicinal chemistry* 2019, **164**:448-470.
38. Boulahjar R, Ouach A, Bourg S, Bonnet P, Lozach O, Meijer L, Guguen-Guillouzo C, Le Guevel R, Lazar S, Akssira M: **Advances in tetrahydropyrido [1, 2-a] isoindolone (valmerins) series: potent glycogen synthase kinase 3 and cyclin dependent kinase 5 inhibitors**. *European Journal of Medicinal Chemistry* 2015, **101**:274-287.
39. Turner SC, Mack H, Bakker MHM, Van Gaalen M, Carolin H, Hornberger W: **1-(quinolin-4-yl)-3-(6-(trifluoromethyl)-pyridin-2-yl) urea and 1-(quinolin-4-yl)-3-(6-(trifluoromethyl)-pyrazine-2-yl) urea derivatives as glycogen synthase kinase 3 (gsk-3) inhibitors for the treatment of neurodegenerative diseases**. In.: Google Patents; 2018.