Glycogen Synthase Kinase 3β Involvement in Neuroinflammation and Neurodegenerative Diseases

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Abstract: ***Background*:** GSK-3β activity has been strictly related to neuroinflammation and neurodegeneration. Alzheimer's disease is the most studied neurodegenerative disease, but GSK-3β seems to be involved in almost all neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, and the autoimmune disease multiple sclerosis.

***Objective*:** This review aims to help researchers both working on this research topic or not to have a comprehensive overview of GSK-3β in the context of neuroinflammation and neurodegeneration.

***Methods*:** Literature has been searched using PubMed and SciFinder databases by inserting specific keywords. A total of more than 500 articles have been discussed.

***Results*:** First of all, the structure and regulation of the kinase were briefly discussed, and then, specific GSK-3β implications in neuroinflammation and neurodegenerative diseases were illustrated with the help of figures, to conclude with a comprehensive overview on the most important GSK-3β and multitarget inhibitors. The structure and IC_{50} values at the target kinase have been reported for all the discussed compounds.

***Conclusion*:** GSK-3β is involved in several signaling pathways in neurons, glial cells and immune cells. The fine regulation and interconnection of all these pathways are at the base of the rationale use of GSK-3β inhibitors in neuroinflammation and neurodegeneration. Some compounds are now under clinical trials. Despite this, the compounds' pharmacodynamic and ADME/Tox profiles were often not fully characterized which is deleterious in such a complex system.

Keywords: Glycogen synthase kinase 3β, neuroinflammation, neurodegeneration, Alzheimer's disease, Parkinson's disease, multiple sclerosis, GSK-3β inhibitors, multitarget ligands.

1. INTRODUCTION

As suggested by the name glycogen synthase kinase-3 (GSK-3), was originally identified in 1980 as a protein kinase involved in the inhibition of glycogen synthase [1]. Insulin signal mediates glycogen synthase activation through dephosphorylation at the residues targeted by GSK-3 [2]. It became clear that this kinase was involved in several cellular processes other than glucose metabolism in a few years. In the early '90s appeared the first articles on its implication in tau (τ) protein phosphorylation and consequently in the neurodegenerative Alzheimer's disease (AD) [3, 4]. Plyte *et al.* wrote such a pioneering review in 1992 on the roles of a simple protein kinase like GSK-3 has on oncogenesis and development [5].

GSK-3's role in regulating the oncoprotein, c-Jun was already known at that time [2]. GSK-3 inhibitors could be promising drugs for treating type 2 diabetes, cancer (including cancer immunotherapy), regenerative medicine, inflammation, cerebral ischemia, psychi-

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atric disorders, infections and neuroinflammation and neurodegeneration represent the topic of this review [6-12]. Among the two isoforms of GSK-3, GSK-3β has attracted more attention as a possible therapeutic target in neuroinflammation and neurodegeneration. First of all, while GSK-3α knockout (KO) mice are viable, GSK-3β KO mice die at the embryonic stage [13]. This proves that the two kinases do not have the same role. Secondly, GSK-3β is more abundant than GSK-3α in the central nervous system (CNS) of rats, and levels of GSK-3β were found to increase with age [14]. For these reasons, GSK-3β is the most studied isoform and the subject of this review. The structure and regulation of the kinase, its implication in neuroinflammation, with an *excursus* on the most implicated signaling pathways, and then specific GSK-3β effects on neurodegenerative diseases will be reported, followed by an overview on the most important inhibitors published to date, giving special attention to those entered in clinical trials.

2. GSK-3β STRUCTURE AND REGULATION

Extensive knowledge of GSK-3β structure and regulation is therefore, a key matter in understanding the enzyme's physiopathological role and in designing potent and selective drug candidates.

The structure of glycogen synthase kinase 3 isoform β was first solved in 2001, and more than 70 crystal structures of human GSK-3β were released in the last 20 years (Table **1**) [15-55].

Table 1. PDB entries for human GSK-3β crystal structures.

PDB Entry	Method	Release Date (YYYY-MM-DD)	Sequence Length	Resolution	Refs.
1GNG	X-ray	2002-10-03	378	2.60 Å	Bax, B. *et al.* [15]
1H8F	X-ray	2002-01-31	352	2.80 Å	Dajani, R. *et al.* [16]
1I09	X-ray	2002-01-01	420	2.70 Å	ter Haar, E. *et al.* [17]
1J1B	X-ray	2003-12-03	420	1.80 Å	Aoki, M. *et al*. [19]
1J1C	X-ray	2003-12-03	420	2.10 Å	Aoki, M. *et al*. [19]
1O9U	X-ray	2003-08-15	350	2.40 Å	Dajani, R. *et al.* [20]
1PYX	X-ray	2003-10-21	422	2.40 Å	Bertrand, J.A. *et al.* [21]
1Q3D	X-ray	2003-10-21	424	2.20 Å	Bertrand, J.A. *et al.* [21]
1Q3W	X-ray	2003-10-21	424	2.30 Å	Bertrand, J.A. *et al.* [21]
1Q41	X-ray	2003-10-21	424	2.10 Å	Bertrand, J.A. *et al.* [21]
1Q4L	X-ray	2003-10-14	424	2.77 Å	Bertrand, J.A. *et al.* [21]
1Q5K	X-ray	2004-08-10	414	1.94 Å	Bhat, R. *et al.* [22]
1R0E	X-ray	2004-10-12	391	2.25 Å	Allard, J. *et al.*[a]
1UV5	X-ray	2004-01-29	350	2.80 Å	Meijer, L. *et al*. [23]
2JLD	X-ray	2008-12-09	420	2.35 Å	Atilla-Gokcumen, G.E. *et al.* [24]
2O5K	X-ray	2007-10-23	372	3.20 Å	Shin, D. *et al.* [25]
2OW3	X-ray	2008.02-19	352	2.80 Å	Zhang, H.C. *et al.* [26]
3DU8	X-ray	2009-03-03	422	2.20 Å	Menichincheri, M. *et al.* [27]
3F7Z	X-ray	2009-03-10	350	2.40 Å	Saitoh, M. *et al.* [28]
3F88	X-ray	2009-03-10	349	2.60 Å	Saitoh, M. *et al.* [28]
3GB2	X-ray	2010-03-02	353	2.40 Å	Saitoh, M. *et al.* [29]
3I4B	X-ray	2010-01-12	414	2.30 Å	Aronov, A.M. *et al.* [30]
3L1S	X-ray	2010-03-02	414	2.90 Å	Arnost, M. *et al.* [31]
3M1S	X-ray	2010-12-22	420	3.13 Å	Atilla-Gokcumen, G.E. *et al.* [32]
3PUP	X-ray	2010-12-22	420	2.99 Å	Feng, L. *et al.* [33]
3Q3B	X-ray	2001-06-15	424	2.70 Å	Coffman, K. *et al.* [34]
3SAY	X-ray	2012-06-13	430	2.23 Å	Cheng, R.K.Y. *et al.*[a]
3SD0	X-ray	2011-08-03	350	2.70 Å	Mesecar, A.M. *et al.*[a]
3ZDI	X-ray	2012-12-26	350	2.64 Å	Fugel, W. *et al.* [35]

(Table 1) contd....

PDB Entry	Method	Release Date (YYYY-MM-DD)	Sequence Length	Resolution	Refs.
3ZRK	X-ray	2011-06-29	371	2.37 Å	Gentile, G. *et al.* [36]
3ZRL	X-ray	2011-06-29	371	2.48 Å	Gentile, G. *et al.* [36]
3ZRM	X-ray	2011-06-29	371	2.49 Å	Gentile, G. *et al.* [36]
4ACC	X-ray	2012-05-16	465	2.21 Å	Berg, S. *et al.* [37]
4ACD	X-ray	2012-05-16	465	2.60 Å	Berg, S. *et al.* [37]
4ACG	X-ray	2012-05-16	465	2.60 Å	Berg, S. *et al.* [37]
4ACH	X-ray	2012-05-16	465	2.60 Å	Berg, S. *et al.* [37]
4AFJ	X-ray	2012-02-29	367	1.98 Å	Gentile, G. *et al.* [38]
4B7T	X-ray	2013-01-30	350	2.77 Å	Tahtouh, T. *et al.* [39]
4DIT	X-ray	2012-02-15	382	2.60 Å	Kim, H.T. *et al.*[a]
4IQ6	X-ray	2013-04-24	426	3.12 Å	Tong, Y. *et al.* [40]
4J1R	X-ray	2013-03-20	424	2.70 Å	Wang, Y. *et al.*[a]
4J71	X-ray	2013-03-20	424	2.31 Å	Wang, Y. *et al.*[a]
4NM0	X-ray	2014-03-26	389	2.50 Å	Stamos, J.L *et al.* [41]
4NM3	X-ray	2014-03-26	389	2.10 Å	Stamos, J.L *et al.* [41]
4NM5	X-ray	2014-03-26	377	2.30 Å	Stamos, J.L *et al.* [41]
4NM7	X-ray	2014-03-26	377	2.30 Å	Stamos, J.L *et al.* [41]
4PTC	X-ray	2015-04-08	441	2.71 Å	Sivaprakasam, P. *et al.* [42]
4PTE	X-ray	2015-04-08	441	2.03 Å	Sivaprakasam, P. *et al.* [42]
4PTG	X-ray	2015-04-08	441	2.36 Å	Sivaprakasam, P. *et al.* [42]
5F94	X-ray	2016-02-03	350	2.51 Å	Luo, G. *et al.* [43]
5F95	X-ray	2016-02-03	350	2.52 Å	Simone, P.D. *et al.* [44]
5HLN	X-ray	2016-05-25	424	3.10 Å	Wagner, F.F. *et al.* [45]
5HLP	X-ray	2016-05-25	424	2.45 Å	Wagner, F.F. *et al.* [45]
5K5N	X-ray	2016-09-21	370	2.20 Å	Liang, S.H. *et al.* [46]
5KPK	X-ray	2018-03-14	424	2.40 Å	Wagner, F.F. *et al.* [47]
5KPL	X-ray	2018-03-14	424	2.60 Å	Wagner, F.F. *et al.* [47]
5KPM	X-ray	2018-03-14	424	2.69 Å	Wagner, F.F. *et al.* [47]
5OY4	X-ray	2017-11-01	420	3.20 Å	Henley, Z.A. *et al.* [48]
5T31	X-ray	2018-02-21	420	2.85 Å	Wagner, F.F. *et al.* [47]
6B8J	X-ray	2017-11-08	420	2.60 Å	Wagman, A.S *et al.* [49]
6GJO	X-ray	2019-03-27	414	2.91 Å	Hoerer, S. [a]
6GN1	X-ray	2018-06-20	368	2.60 Å	Tesch, R. *et al.* [50]
6H0U	X-ray	2019-05-15	420	2.30 Å	Redenti, S. *et al* [51]
6HK3	X-ray	2019-07-17	350	2.35 Å	Gobbo, D. *et al.* [52]
6HK4	X-ray	2019-07-17	350	2.50 Å	Gobbo, D. *et al.* [52]
6HK7	X-ray	2019-07-17	347	3.20 Å	Gobbo, D. *et al.* [52]
6TCU	X-ray	2020-09-16	355	2.14 Å	Prati, F. *et al.* [53]
6V6L	X-ray	2020-01-15	420	2.19 Å	Ramurthy, S. *et al.* [54]
6Y9R	X-ray	2020-05-20	350	2.08 Å	Buonfiglio, R. *et al.* [53]
6Y9S	X-ray	2020-05-20	350	2.03 Å	Buonfiglio, R. *et al.* [55]
7B6F	X-ray	2020-12-16	365	2.05 Å	Tesch, R. *et al.*[a]

[a] Structure deposited on PDB but not published.

There are two widely recognized highly homologous GSK-3 mammalian isoforms, α and β, encoded by two different genes with different chromosomal locations. GSK-3α is a protein of 51 kDa while the β iso-

form has a mass of 47 kDa, and they differentiate, particularly in the last 76 C-terminal residues with only 36% of homology. The kinase domain contains motifs typical of all protein kinases, and it is highly conserved (98% of homology) within the two different isoforms. Therefore, the overall similarity is 85% [2].

Given the high homology of the catalytic domain and the ATP binding site, the selective inhibition of one of the isoforms is still anything but trivial. However, recently, an Asp-Glu switch between GSK-3α and GSK-3β (Asp133 for GSK-3β and Glu196 for GSK-3α) made it possible to identify the selective inhibitors [47].

Human GSK-3β is encoded by the gene GSK3B (chromosomal location: 3q13.33), and it is ubiquitously expressed in all mammalian tissues. Three different mRNA transcript variants derive from the human GSK3B gene [56, 57]. The mRNA transcription results in two different isoforms, GSK-3β1 for transcript variants 1 and 3 and GSK-3β2 for transcript variant 2. In particular, the alternative splicing between exon 8 and exon 9 in transcript variant 2 generates an additional insert of 13 amino acids within the catalytic domain thus GSK-3β2 is longer (49 kDa) than GSK-3β1 [58]. It should be noted that GSK-3β2 is primarily expressed in neurons and is involved in various neuronal functions such as axon growth [59].

The GSK-3 family, along with cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), and cdc2-like kinase (CLK), are members of the CMGC kinase group [60, 61]. As a Ser/Thr specific kinase, GSK-3β shares the classic bilobal structure: seven antiparallel β-strands packed together forming a closed β-barrel and only one α-helix form the smaller N-terminal domain (residues 25-134). The α-helix connecting the fifth and sixth strand consists of only two turns and is shorter than other kinases. Instead, the catalytic C-terminal domain (residues 135-380) mainly comprises α-helices (Fig. **1**) [16, 62]. The hinge region connects two major domains, and the deep cleft between the two lobes is recognized as the catalytic site. It is responsible for binding and orienting both ATP and the protein substrate, as well as transferring the γ-phosphate group from the phosphate donor to the serine or threonine acceptor residue. The ceiling of the catalytic cleft is delimited by the typical glycine-rich loop conserved among the kinome and contains the consensus motif GXGXXGXV, which for GSK-3β lies between Gly63 and Val70. This loop is organized into a flexible β-strand-turn-β-strand structure that covers and anchors ATP's α and β-phosphate [63]. A lysine residue (Lys85) located in the upper part of the active site is responsible for binding the ATP's non-transferable phosphate groups and for catalyzing the transfer of the γ-phosphate group to the substrate [64]. In addition, a salt bridge between Lys 85 and Glu 97 (located in the α-helix of the N-lobe) helps stabilize the active conformation of the kinase [17, 61, 63].

The activation loop defines the surface of the substrate-binding pocket, also named T-loop (residues 200-226). The triplet DFG (Asp200 – Phe201 – Gly202) occupies the N-terminal part of the loop, while the C-terminal portion contains the APE (Ala224 – Pro225 – Glu226) motif. In the active form of the enzyme, the activation segment has an extended conformation in which the aspartic acid side chain in the DFG motif is directed towards the ATP binding pocket and is capable of chelating the metal ion (Mg^{2+}) and helping to orient the terminal phosphate group [63]. This active kinase conformation is also known as DFG-*in*, while in the inactive state the Asp residue of the DFG motif points out of the ATP binding site and the conformation is called DFG-*out* [61].

Within the activation loop, a tyrosine residue, Tyr216, is constitutively phosphorylated in the enzyme active state, similar to MAPKs that require double phosphorylation within the T-loop for activation. Indeed, while GSK-3β requires only the phosphorylation of the Tyr residue for its activation, in MAPKs, besides the Tyr residue, an additional threonine residue has to be phosphorylated [65, 66]. Accessibility to the substrate binding cleft is promoted by rotation of the phosphorylated Tyr216 side chain moving out of the pocket [16, 17]. As for the phosphorylation mechanism of this residue, several have been reported, but the most reliable is that of intramolecular autophosphorylation during the protein folding process [67]. However, it seems that the phosphorylation of the tyrosine residue may increase the enzyme activity (5-fold increase), but it is not strictly essential for kinase activity [16]. In addition to Tyr216, several phosphorylation events are responsible for regulating GSK-3β activity. In particular, the modification of serine or threonine residues within the N-terminus and the C-terminus of the kinase by other kinases or autophosphorylation events may inactivate the kinase.

A prominent role is played by Ser9 since its phosphorylation by other kinases results in enzyme inactivation. In particular, the N-terminal tail of GSK-3β with phosphorylated Ser 9 is able to competitively block the access to the substrate pocket to the primed substrates [68, 69]. Primarily responsible for the negative phosphorylation is protein kinase B (Akt/PKB) as part of the insulin pathway, but many other kinases have been shown to be responsible for phosphorylation, including

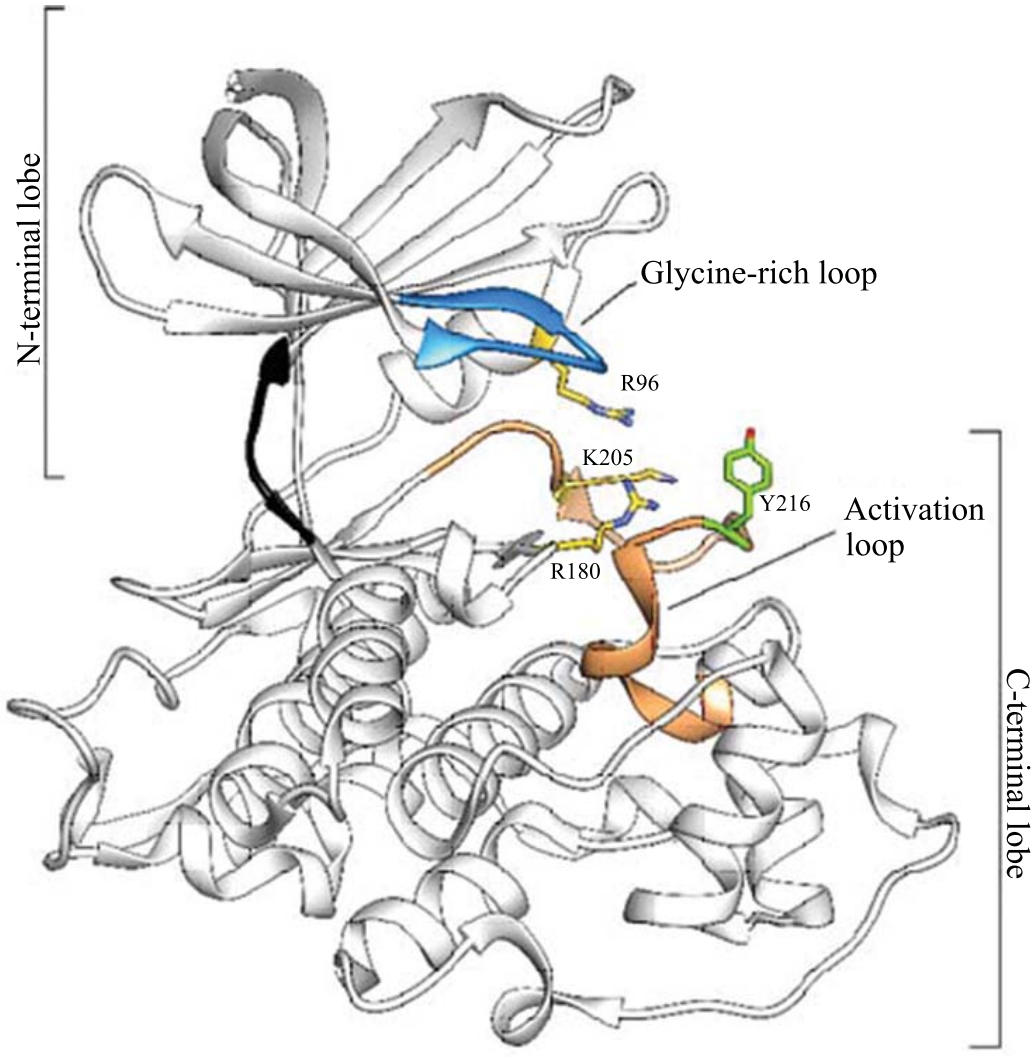


Fig. (1). Three-dimensional representation of GSK-3β structure. The N-terminal portion is depicted in the upper part while the C-terminal lobe occupies the lower part of the image. The black section represents the hinge region which connects the two major kinase domains and defines the catalytic task. The glycine-rich loop delimiting the catalytic cleft is in blue. The activation loop is shown in orange. Yellow residues are the basic triad responsible for promoting the interaction with primed substrates. The constitutively phosphorylated Tyr 216 residue is shown in green. Ser9 was not displayed because PDB 6H0U, used for this image, is truncated at residue 35.

protein kinase A (PKA), protein kinase C (PKC), AGC kinases, p70 ribosomal S6 kinase, p90 ribosomal S6 kinase [70-72]. Recently, to study the key role of Ser9 phosphorylation, novel antibodies capable of recognizing non-phosphorylated Ser9 GSK-3β have been developed and thanks to them it was demonstrated that GSK-3β reactivity correlates with enzymatic activity and that protein phosphatase inhibition decreases the non-phosphorylated GSK-3β levels and the enzymatic activity in cells [73].

Other phosphorylation events that have been demonstrated to inhibit GSK-3β activity are the ones catalyzed by p38 MAPK on Ser389 and Thr390. The C-terminal tail of GSK-3β with phosphorylated serine or threonine residues, as at Ser9, could mimic the primed substrate and inactivate the enzyme [74]. It was also demonstrated that Erk-mediated phosphorylation of Thr43 leads to GSK-3β inactivation, since this phosphorylation primes GSK-3 for Ser9 phosphorylation by the p90 ribosomal S6 kinase [75]. However, while the phosphorylation of Ser or Thr residues remains the major regulation mechanism, others have been reported. For example, Lys183 acetylation decreases GSK-3β activity by preventing ATP access to the binding site [76]. Moreover, other posttranslational modifications like mono-ADP-ribosylation and citrullination

are responsible for kinase inhibition and nuclear localization [77, 78].

The regulation of GSK-3β activity can be also affected by the formation of protein complexes as found in the Wnt and Hedgehog pathways [79, 80]. In fact, GSK-3β localization both in the nucleus and/or in protein complexes directs kinase activity towards specific substrates, thus regulating GSK-3β selectivity.

Notably, the presence of a cysteine residue located right before the DFG peptide (Cys199) could be exploited as a nucleophile point to target the kinase with covalent inhibitors [51]. Cysteine residues close to the DFG motif are accessible to form covalent bonds and the presence of polar residues (*e.g.* Asp residue from the DFG triplet and a catalytic Lys in the ceiling of the binding site) near the nucleophile target allows to design also irreversible covalent inhibitors [81].

The consensus amino acid sequence that GSK-3β generally recognizes is Ser/Thr-X_1-X_2-X_3-(P)Ser/Thr, where (P)Ser/Thr stands for a pre-phosphorylated residue of serine or threonine, and X_1 is often a proline, although not strictly required [64].

Thus, GSK-3β substrates require the action of a priming kinase that phosphorylates the C-terminal serine/threonine residue and allows the phosphorylation of the N-terminal serine or threonine that is located 4 residues upstream [82]. A triad of basic residues (Arg96, Arg180, Lys205) support GSK-3β in the interaction with the "primed" substrate forming a phosphate binding pocket [16, 17, 69, 83]. Even if priming phosphorylation is a mandatory requirement for GSK-3β substrates, the kinase is able to phosphorylate a limited number of non-primed substrates: c-Jun, c-Myc, histone H1.5 and MARK2/PAR-1. In these proteins, acidic residues or peptide conformations replace the priming phosphate in GSK-3β substrate recognition [84-86].

3. GSK-3β IN NEUROINFLAMMATION

Neuroinflammation is an inflammatory condition that occurs in the CNS and, as a consequence, involves cerebral innate immune cells, mainly astrocytes and microglia. Neuroinflammation is a physiological, beneficial response necessary to ensure a healthy CNS, as it is responsible for the phagocytosis of dead cells and the production of mediators essential for neuronal function and neurogenesis. Similarly to peripheral inflammation, sustained neuroinflammation could become detrimental in certain conditions, leading to impaired neuronal function and cell death [87, 88]. Peripheral immune cells are not completely excluded from the process because when inflammation impairs the permeability of blood-brain barrier (BBB), macrophages, lymphocytes, and neutrophils could reach CNS [89]. Neuroinflammation has been reported in many neurodegenerative diseases including AAD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and in the multiple sclerosis (MS) autoimmune disease [88, 90-93].

GSK-3β is involved in both peripheral and central inflammation, where it has been found to be crucial in mediating the inflammatory responses in both microglia and astrocytes [94-96]. In addition to controlling the innate immune system, GSK-3β is an important regulator of adaptive immunity, which contributes to the overall pro-inflammatory effect [97]. GSK-3β is involved in the activation and migration of glial cells [94], as well as in differentiation of T cells (*e.g.* Th17 cells) [98]. From the point of view of the mechanism, GSK-3β activates the pro-inflammatory NF-κB, c-Jun kinase (JNK), and signal transducer and activator of transcription 3 (STAT3) pathways, blocks the cyclic AMP response element binding protein (CREB) and β-catenin anti-inflammatory pathways and has both pro- and anti-apoptotic effects.

3.1. Wnt Signaling Pathway

In microglia and other immune cells, activation of the canonical Wnt signaling pathway alleviates neuroinflammation [99-102]. GSK-3β is a negative regulator of the canonical Wnt signaling pathway involving β-catenin (Fig. **2**) [103]. In the absence of Wnt ligands, GSK-3β forms the β-catenin destruction complex with axin, adenomatous polyposis coli (APC), and Casein kinase 1-alpha (CK-1α). The complex between APC, AXIN and kinases, and β-catenin engagement are ensured by different repeats on the protein members and by kinase-mediated phosphorylation of both axin and APC [104-106]. Recruited β-catenin undergoes phosphorylation at Ser45 by CK-1α, priming β-catenin to subsequent GSK-3β polyphosphorylation at residues Ser33, Ser37 and Thr41, which improves its interaction with the destruction complex and prompts it for the recognition by β-Transducin Repeat Containing E3 Ubiquitin Protein Ligase (β-TrCP). β-TrCP catalyzes β-catenin polyubiquitylation at Lys19, responsible for its recognition by the ubiquitin-proteasome system and subsequent degradation [107-109]. Instead, when Wnt ligand is present, it binds to membrane receptor Frizzled and co-receptor lipoprotein receptor-related protein 5 or 6 (LRP5/6), which leads to the phosphorylation and activation of disheveled (DVL) that recruits both axin and GSK-3β, suppressing their activity on β--catenin [109, 110].

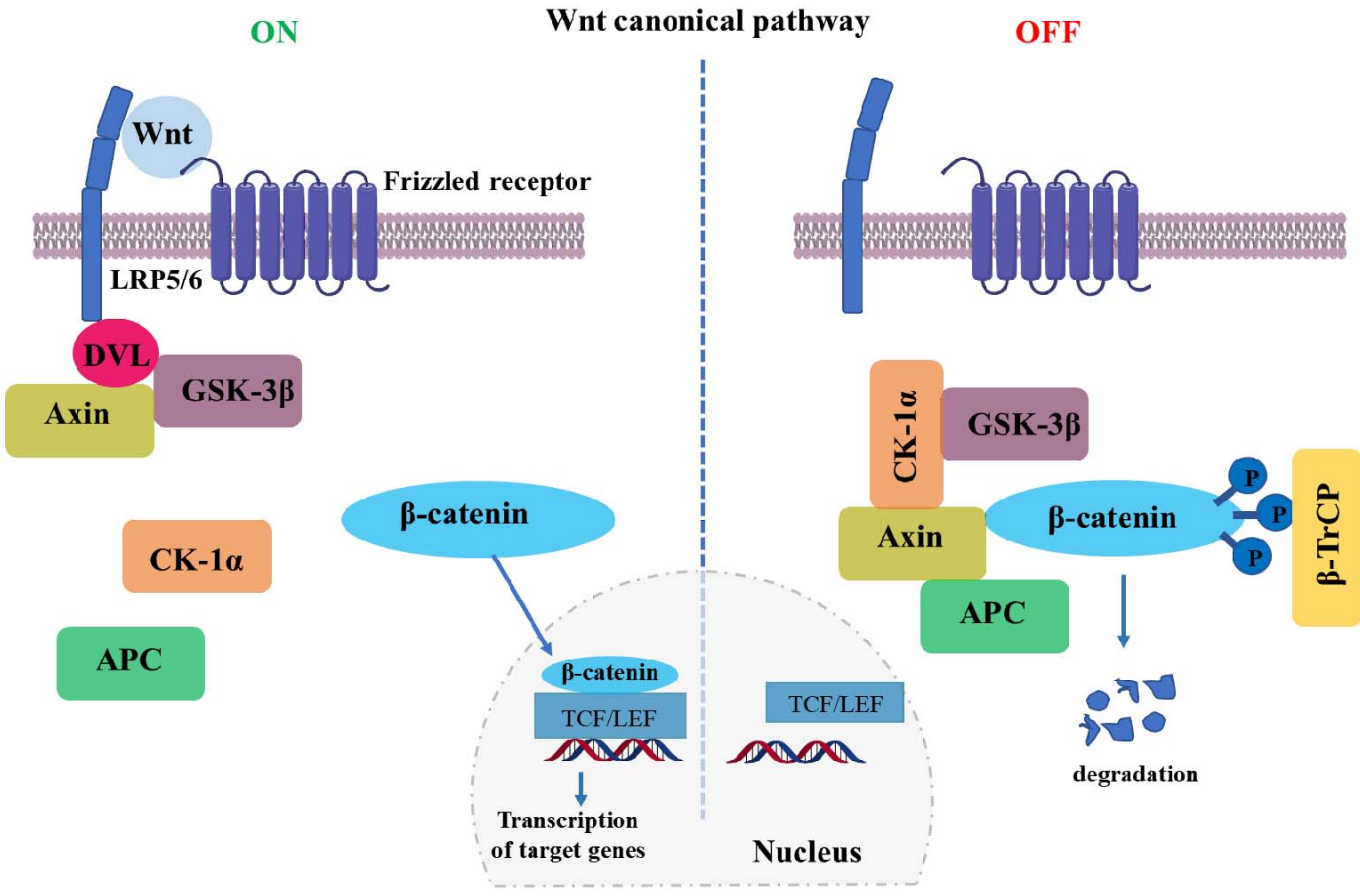


Fig. (2). GSK-3β involvement in Wnt canonical pathway. On the left: In the presence of Wnt ligand, activation of Frizzled receptor and LRP5/6 impedes the formation of the β-catenin destruction complex also by DVL-mediated recruitment of axin and GSK-3β. Stabilized β-catenin can enter the nucleus and interact with transcription factors regulating the expression of target proteins. On the right: In the absence of Wnt ligand, GSK-3β forms the β-catenin destruction complex with CK-1α, APC, and axin. CK-1α phosphorylates β-catenin followed by GSK-3β, allowing β-catenin recognition by β-TrCP that through polyubiquitylation signals β-catenin for degradation, impeding its entrance into the nucleus.

Free stabilized β-catenin protein enters now the nucleus to bind different transcription factors, which include T-cell factor/lymphoid enhancer factor (TCF/LEF), T-box transcription factor 5 (TBX5), and hypoxia-inducible factor 1α (HIF-1α). In particular, TCF/LEF is involved in the regulation of cell differentiation and proliferation, promoting the expression of genes, such as c-Myc, cyclin D2, tumor necrosis factor α (TNF-α) and CD44 [111, 112]. Noteworthy, LRP5/6 is phosphorylated by GSK-3β and by different CK isoforms on Ser1490 and Thr1479, Thr1493, respectively, leading to axin recruitment and stabilization [107]. Interestingly, β-catenin activation by GSK-3β inhibition was found to stabilize BBB. In particular, GSK-3β inhibition enhanced p-glycoprotein expression and promoted tight junction stability in brain endothelial cells in a β-catenin-dependent manner [113, 114]. Furthermore, when the same cells were stimulated by cytokines, GSK-3β inhibition reduced adhesion molecule expression, monocyte adhesion to cells, and migration across them, but it has not been reported whether this involved β-catenin [115].

3.2. NF-κB Signaling Pathway

The most known implication of GSK-3β in the inflammatory response is its ability to interact directly with NF-κB [116]. NF-κB is a family of five transcription factors (p50, p52, p65, RelB, and c-Rel) which act at DNA level as homo- or hetero-dimers [117]. In the resting state, NF-κB are sequestered in the cytoplasm by inhibitors of κB (IκB) (Fig. **3**) [118]. Activation of NF-κB is obtained by IκB degradation, which allows

the free dimers to enter the nucleus and mediate the expression of several pro-inflammatory cytokines (*i.e.*, TNF-α and interleukins IL-1β, IL-6, and IL-12) and other inflammatory factors such as cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) [117, 119-121]. IκB degradation is mediated by the multimeric IκB kinase (IKK), which is composed by two catalytic subunits (IKKα and IKKβ) and a regulatory subunit called NF-κB essential modulator (NEMO) [122]. GSK-3β is involved in NF-κB signaling pathway at different levels: *i*) direct phosphorylation of NF-κB members; *ii*) IKK activation and subsequent IκB phosphorylation (*e.g.* degradation) [123]; *iii*) degradation of β-catenin [124]; *iv*) NEMO phosphorylation (Fig. **3**) [125].

Different NF-κB members are substrates of GSK-3β (*i.e.*, p65, RelB and the precursors p100 and p105), where p65 was described to be phosphorylated to multiple residues that correlates with an enhanced binding to specific genes leading to their increased expression [126-128]. In particular, phosphorylated p65 shows an enhanced association with CREB-binding protein (CBP), and this is responsible for p65-increased DNA binding [129-131]. Conversely, it has been found that phosphorylation of RelB regulates its degradation and the phosphorylation of p100 and p105 modulates their stability and digestion [132, 133]. Instead, β-catenin was found to bind directly to p65/p50-containing NF-κB dimers, reducing DNA binding, thus GSK-3β can influence NF-κB activity due to its involvement in the regulation of β-catenin levels in the Wnt signaling pathway [124]. GSK-3β-mediated NEMO phosphorylation is necessary for correct and ordered NF-κB activation [125]. It should be noted that also an excess of GSK-3β activity was found to reduce IKK activation and IκB degradation, demonstrating the fine regulation of the pathway [134]. Globally, the aforementioned observations support the use of GSK-3β inhibitors to decrease NF-κB mediated inflammatory response.

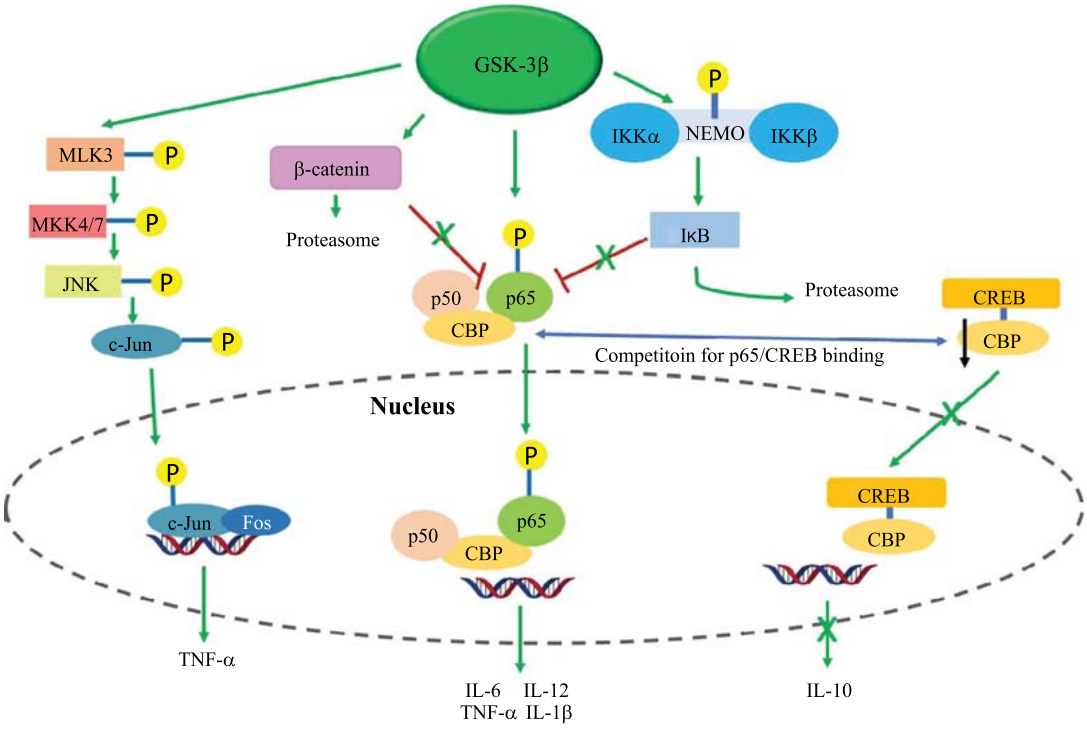


Fig. (3). GSK-3β involvement in JNK, NF-κB, and CREB signaling pathways. GSK-3β activates MLK3 that initiates a cascade of phosphorylation that through MKK4/7 and JNK, leads to c-Jun activation, that is part of the AP-1 transcription factor regulating target genes, including TNF-α gene. In the NF-κB pathway, GSK-3β activates the NF-κB monomer p65 to bind to p50 and CBP, phosphorylates NEMO mediating IκB degradation and impedes β-catenin-mediated reduction of p65 DNA binding affinity by stimulating its degradation in Wnt canonical pathway. All these effects lead to translocation of NF-κB (p50/p65) in the nucleus with expression of pro-inflammatory cytokines IL-1β, IL-6, IL-12 and TNF-α. Due to the limited amounts of CBP available in the cell following GSK-3β activation, CREB-CBP complex levels are lowered and consequentially its effect on the expression of anti-inflammatory IL-10 is reduced.

3.3. CREB Signaling Pathway

Tightly related to GSK-3β regulation on NF-κB pathway is the influence of GSK-3β on the activation of another critical transcription factor, CREB. As NF-κB (*e.g.* p65), CREB activation is triggered by the association with CBP and they compete for the same binding site [135, 136]. CBP is present in a limited amount in the cell nucleus and if phosphorylated p65 is present in higher amounts, CBP is consequentially sequestrated from interaction with CREB (Fig. **3**) [130]. CREB plays a crucial role in mediating the expression of the anti-inflammatory cytokine IL-10 [137], as well as several other genes critically involved in neuronal development, protection, and plasticity (*i.e.*, growth factors, transcription factors, signal transduction factors, and metabolic enzymes) [138]. It should be noted that CREB is itself a GSK-3β substrate, and its phosphorylation at Ser-129 was found to decrease and increase CREB-mediated gene expression [138-141].

NF-κB and CREB signaling pathways are regulated by toll-like receptors (TLRs) [142]. TLRs, critical for evoking innate immune responses, are members of pattern recognition receptors (PRR), which are activated by pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) [143]. In particular, TLR2/4 are activated by LPS and NF-κB, and CREB regulation follows a MyD88-dependent pathway [144]. Astrocytes, oligodendrocytes, and microglia, but also neurons, express toll-like receptors (TLR) on their surface [145]. Interestingly, the activation of TLR2/4 also triggers the phosphatidylinositol-3-kinase (PI3K) pathway, thus activating Akt that, in turn, deactivates GSK-3β through phosphorylation at Ser9, adding another point of regulation for NF-κB and CREB activities [130, 144, 146]. GSK-3β was found to be involved also in pro-inflammatory response mediated by TLR3 pathway [147]. The interconnections between TLR and Wnt signaling pathways are important to ensure a fine modulation of the inflammation process, thus confirming that GSK-3β plays a crucial role due to its involvement in multiple steps of both pathways [102, 148].

3.4. STAT3/5 Signaling Pathway

Another effect of GSK-3β (and not GSK-3α) in neuroinflammation is mediated by the direct activation of STAT3 and STAT5. STAT3 is known to be responsible for the amplitude and duration of the inflammatory response [149, 150]. GSK-3β acts by promoting STAT3 association with the interferon-γ (IFNγ) receptor-associated intracellular signaling complex responsible for STAT3 activation [151]. STAT3 is a transcription factor that in stimulated glia was found to promote IL-6 production, thus mediating a pro-neuroinflammatory response *via* GSK-3β-mediated activation [152]. In addition, GSK-3β-dependent STAT3 activation is responsible for IL-9-mediated enhancement of T helper 17 (Th17) cell differentiation. Th17 cells are responsible for neuroinflammation in neurodegenerative diseases (*i.e.*, AD, PD, and MS) as well as in several neurological and psychiatric diseases [153, 154].

3.5. JNK Signaling Pathway

During nerve growth factor (NGF) withdrawal-induced cell death in PC-12 cells, GSK-3β showed to regulate the JNK pathway, by phosphorylation-mediated activation of mixed lineage kinase 3 (MLK3) activity (Fig. **3**) [155]. MLK3 phosphorylates MAPKs, MKK4 and MMK7, leading to their activation which results in the phosphorylation of the MAPK JNK, and finally of c-Jun. c-Jun is a member of the transcription factor activated protein-1 (AP-1) responsible for TNF-α production [155, 156]. Wang *et al.* proposed a different mechanism of action: MLK3 works as a dimer, and in LPS-stimulated microglia, the authors found that inhibition of GSK-3β disrupts MLK3 ability to dimerize, preventing *de facto* its activity [157].

3.6. Apoptosis

Apoptosis is crucial for maintaining homeostasis in the human body. In fact, abnormal apoptosis is associated with the disease. Cancer and autoimmune diseases are characterized by poor apoptosis, while an excess of apoptotic processes is a feature of neurodegenerative diseases. Several independent studies reported that GSK-3β promotes apoptosis in AD, PD, ALS and Huntington's disease (HD) [158-163]. The common apoptotic pathways are the mitochondria-mediated intrinsic and death receptor-mediated extrinsic pathways [164]. GSK-3β is involved in both pathways but with the opposite effects. The intrinsic pathway is positively regulated by GSK-3β, and it is evoked by a myriad of stimuli which comprise DNA damage, oxidative stress, and endoplasmic reticulum (ER) stress. The result is a modification in Bax protein conformation that causes Bax translocation to the mitochondrial membrane where it can interact with Bcl-2 and disrupt the mitochondrial membrane potential by oligomerization. This resulted in the release of pro-apoptotic proteins such as cytochrome c. Cytochrome c forms the aptosome by binding to other proteins that lead to activation of caspase-9 and consequently, of the caspase cascade that starts with cleavage-mediated caspase 3 activation and finishes with death of the cell [160]. GSK-3β is involved in multiple steps targeting Bax, Bim, Bcl-2, and

voltage-dependent anion-selective channel (VDAC), thus contributing to the disintegration of the mitochondria [165-172]. In particular, GSK-3β activates pro-apoptotic transcription factor p53 leading to enhanced expression of Bax and inhibiting CREB, which is instead involved in anti-apoptotic Bcl-2 expression [130, 169, 173-177]. In addition, GSK-3β decreases the levels of the pro-survival β-catenin [103]. Heat shock factor 1 (HSF-1) represents another substrate of GSK-3β, inhibited by the phosphorylation process. HSF-1 is a key transcription factor for protective heat shock proteins, whose reduced expression can facilitate apoptosis [178]. GSK-3β has also a central role in microtubule stability, as well described in the neurodegenerative diseases part of this review. When phosphorylated by GSK-3β, the τ protein dissociates from microtubules that are thus destabilized, opening the way to the structural modification of the cell that occurs during apoptosis [179, 180]. Thus, there is not a unique step in the intrinsic pathway responsible for the pro-apoptotic activity of GSK-3β, but rather a fine regulation in several interconnected processes. In addition, it is clear that GSK-3β is not an apoptosis initiator and that, in physiological conditions, GSK-3β does not lead to apoptosis, while in pathological conditions, when apoptosis has been initiated by insulting stimuli, GSK-3β activity facilitates the apoptotic process through the intrinsic pathway. Therefore, growth factor-dependent survival depends on the activation of the PI3K pathway that triggers Akt, which inactivates GSK-3β by phosphorylation at Ser9 [181].

On the other hand, the extrinsic apoptotic pathway requires activation of the so-called death receptors (DRs). These receptors are members of the TNF family of receptors and specific ligand activation consists in their homo-trimerization. After that, recruitment of FADD (Fas-associated death domain protein) and procaspase-8 and procaspase-10 in the cytoplasmic portion forms the death-inducing signaling complex (DISC). As a consequence, caspase-8 results activated and, in turn, activates effector caspases (*i.e.*, caspases 3, 6 and 7) [182]. Several studies reveal that GSK-3β is capable to inhibit DRs-mediated apoptosis upstream to caspase-8 [160]. Accordingly, GSK-3β has been found in an anti-apoptotic protein complex associated with DRs together with DEAD-box RNA helicase 3 (DDX3) and cellular inhibitor of apoptosis protein-1 (cIAP-1). The complex caps the DR, thus preventing DISC formation and blocking pro-apoptotic signaling [183].

Among the inflammatory stimuli, oxidative stress should be mentioned that, as previously reported, could also lead to apoptosis. Akt is strongly inhibited by reactive oxygen species (ROS), thus leading to GSK-3β in its active form that signals NrF2 for degradation [10]. NrF2 is a key transcription factor for protection against oxidative stress, in fact, it controls the expression of proteins involved in detoxification of electrophiles, free radical and glutathione metabolism, and proteasome function [184].

3.7. Neuropolarization

Even if not strictly related to neuroinflammation, neuropolarization is essential to maintain neuronal physiological actions. It is important to mention that GSK-3β, highly expressed in the *hippocampus*, an important brain area that regulates learning and memory, is able to control synaptic polarization by its coordination and interconnection in several pathways such as PI3K, CRMP-2, and TSC-mTOR (mechanistic target of rapamycin). Its essential role in neuronal morphogenesis contributes to the activity, extension, and branching of neurons that are essential in the preservation of central physiological actions. Thus, neuronal polarity represents a possible target in neurological diseases since mutations in many polarity genes are connected with dysfunctions in cytoskeletal products in different neurodegenerative disorders such as PD and AD [185]. In particular, reduced activity of GSK-3β leads to an improvement in neuronal growth, while the activation of this attributed kinase results in the phosphorylation of CRMP-2 in Thr514 contributing to the insurgence of neurodegeneration [186, 187].

3.8. Multiple Sclerosis

The specific involvement of GSK-3β in neurodegenerative diseases other than the neuroinflammatory process will be discussed in the following paragraphs. The rationale for the use of GSK-3β inhibitors in the treatment of MS is entirely based on the neuroinflammatory pattern of this autoimmune disease [112, 188]. For this reason, it will not be discussed further below. MS is an autoimmune disease that is characterized by demyelination and the appearance of neuroinflammatory lesions featured by T cells and microglia [189, 190]. Results obtained from different research groups suggested that the process of demyelination determines impairments in axon regulation causing dysfunction of mitochondrial activity [189, 190]. Noteworthy, in a study on 319 patients with MS, an increased frequency of the rs334558 GG genotype (the common variants are four: rs2199503, rs9826659, rs334558 and rs6438552) was observed in patients with relapsing-remitting MS. Therefore, rs334558 is a susceptibility factor for MS and, due to its localization in the promoter region, it has been suggested to influence the gene transcription rate [191].

4. GSK-3β IN NEURODEGENERATIVE DISEASES

4.1. Alzheimer's Disease

AD is characterized by *dementia* and progressive loss of memory, cognitive functions including language, and failure in performing simple and daily activities [192, 193]. Hallmarks of the disease are the formation of senile plaques composed of amyloid β protein (Aβ) and neurofibrillary tangles (NFTs) consisting of hyperphosphorylated τ protein. The neurodegeneration characterized by neuronal loss is accompanied by the neuroinflammatory process, oxidative stress, and several cellular abnormalities [194].

GSK-3β is involved in synaptic plasticity that regulates learning and memory, and it is well known that impairments in synaptic plasticity determine memory deficits displayed by patients affected by AD [186, 195, 196]. Long-term potentiation (LTP) and long-term depression (LTD), two types of long-term changes, are models at the base of synaptic plasticity: the activation of N-methyl-D-aspartate receptors (NMDARs) triggers the induction of LTP and LTD at the postsynaptic level [197, 198]. Chen *et al.* reported that GSK-3β is connected to NMDARs; arguing with their work that inhibitors of this kinase protein determine the decrease of NMDARs current *via* internalization of the same receptors mediated by Rab5 (Ras analog in the brain)/clathrin [199]. An alteration of LTP is demonstrated in AD transgenic mice as well as alterations in spatial learning in models that overexpress GSK-3β in the *hippocampus* area. An opposite effect of GSK-3β is described by Hooper and Zhu *et al.* demonstrating its involvement in different signaling pathways that regulate the NMDARs' outcomes; it is able to induce inhibition of LTP by an impairment in the release of the neurotransmitter glutamate (*e.g.*, the ligand of NMDAR) [200, 201]. The regulation of glutamate delivery is controlled by Synapsin I (SynI): its expression results inhibited by GSK-3β that also reduces the levels of different synaptic proteins [200]. The stimulation of LTP leads to the involvement of the PI3K/Akt signaling pathway in which Akt is able to inhibit GSK-3β [202]. Activation of PI3K followed by the phosphorylation of its substrate phosphatidylinositol-4,5-bisphosphate (PIP2) primes the release of phosphatidylinositol-3,4,5-trisphosphate (PIP3) that targets PDPK1 (phosphoinositide-dependent kinase 1) activating it to phosphorylate Akt at Thr308. Akt is contemporarily activated by phosphorylation at Ser473 by mTOR2. Activated Akt phosphorylates GSK-3β at Ser9, leading to its inactivation [203, 204]. GSK-3β is activated in LTD through NMDAR activity, but it is also required for its inducement [205]. According to Mulkey *et al.*, the signaling pathway involves the initial change in calcium concentration, the activation of calcineurin, a protein calcium-calmodulin-dependent, that goes to activate protein phosphatase 1 (PP1) inducing dephosphorylation in Ser9, and thus activating GSK-3β [206]. The relationship between synaptic plasticity and GSK-3β is understandable by the signaling pathway shared between LTP and LTD: since a decrease of LTP is correlated to an impairment in synaptic plasticity, LTP is unable to inhibit LTD resulting in a hyperactivation of GSK-3β [202].

One of the pathological features that characterize the pathology of Alzheimer's disease is the development of Aβ plaques: the disfunction and damage in the neuronal compartment caused by the production of NFTs, triggered by pathological hyperphosphorylation of τ protein, are initiated by the formation and accumulation of Aβ plaques that lead to cell death and dysfunctions [207]. The event that initiates the trigger points of the pathology is debated: Lewis and co-workers reported an experiment conducted on a line of transgenic mice that express a mutant form of τ and a line of transgenic mice expressing mutated Amyloid Precursor Protein (APP); the results suggested that both τ protein and Aβ lead to the development of NFTs [208]. However, the presence of Aβ determines the switch of τ-mediated effects into toxic effects and impairs the formation of NFTs due to caspases activation leading to τ cleavage [209-211]. Aβ induces a loss of τ binding affinity for microtubules [212, 213]. Aβ formation starts with the cleavage of APP, a trans-membrane protein, performed by α-secretase or β-secretase. α-Secretase leads to soluble APPα (sAPPα) and α-C terminal fragment (α-CTF), while sAPPβ and β-CTF are the products of β-secretase-1 (BACE1) [214]. Both α and β CTFs are substrates of γ-secretase that leads to p3 and Aβ peptides, respectively. While p3 is rapidly degraded, Aβ tends to accumulate in the extracellular space to form senile plaques leading to neuronal loss and cell dysfunction. Thus, α-secretase mediates the non-amyloidogenic APP pathway and β-secretase the amyloidogenic one (Fig. **4**) [215]. GSK-3β is known as a regulator of BACE-1 expression: *in vitro* experiments suggest that GSK-3β-knockdown reduces BACE-1 mRNA levels *via* the NF-κB pathway and, as a consequence, decreases the Aβ deposition [216]. Aβ peptides could be of different lengths (from 38 to 49 residues) where Aβ40 and Aβ42 represent the main forms. Of these two, the last is more prone to form aggregates [214, 217]. γ-secretase is a protein complex whose catalytic activity is mediated by its subunit presenilin 1 (PS1). Mutations at the level of the PS1 gene could

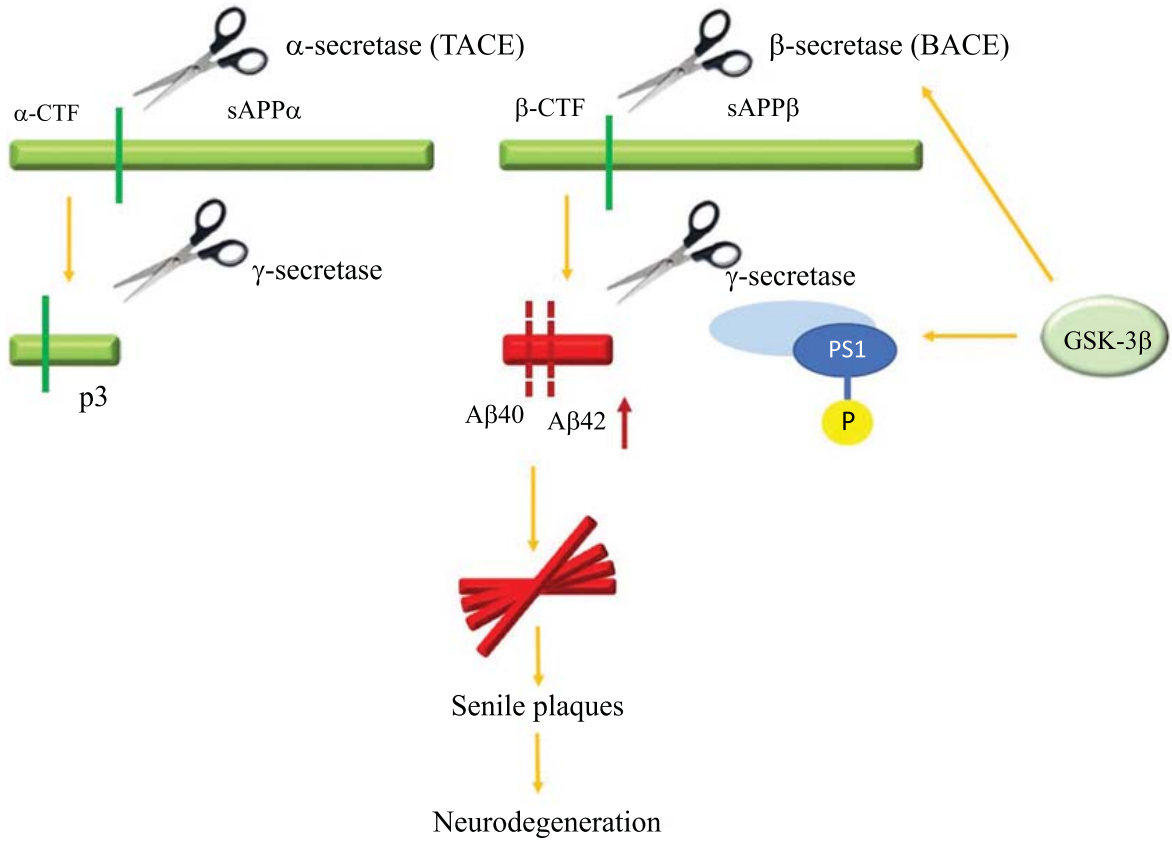


Fig. (4). The cleavage of APP by α-secretase and β-secretase is shown in the figure. The fragments α/β-CTFs are then cleaved by γ-secretase developing p3 and Aβ peptides, respectively. GSK-3β determines the phosphorylation of PS1, a catalytic subunit of γ-secretase, resulting in an increased production of Aβ42. Aβ peptides tend to accumulate in senile plaques, one of the hallmarks of AD.

determine an increased production of Aβ42 [218]. PS1 can be phosphorylated by GSK-3β in Ser353 and Ser357, and this phosphorylation state mediates the reduction of Aβ40 production and the decreased Aβ40/Aβ42 ratio. According to Maesako *et al.*, the level of GSK-3β-mediated phosphorylated PS1 is increased in sporadic AD brains, contributing to lead to neurodegeneration [219].

Microtubule-associated τ protein is expressed at the central level in neurons and axons and plays physiological roles in the preservation of cellular functions stabilizing microtubules [220, 221]. The six isoforms of the τ protein diversify according to a different number of microtubule-binding repeats in the primary structure (3 repeats, 3R or 4 repeats, 4R) [220]. An important feature concerning the structure of τ protein is the possibility of posttranslational alterations of particular residues by different types of reactions: phosphorylation, deamidation, acetylation, methylation, O-glycosylation, and ubiquitylation [222]. Hyperphosphorylation of residues located in microtubule-binding domains causes a τ reduced ability to bind and stabilize microtubules determining a changed 4R/3R τ ratio and accumulation of misfolding hyperphosphorylated τ proteins that self-assemble in pathological intracellular paired helical filaments (PHFs) creating the NFTs (Fig. **5**) leading to neuronal loss [223-227]. However, according to Kimura *et al.*, the synaptic and neuronal loss occurred before the formation of NFTs. The authors performed an experiment using two lines of mice; the first type of mice expressed human τ protein, while the second type expressed the aggregation form of τ protein. What is clear from this test is the appearance of synaptic loss in the presence of the phosphorylated τ protein while neuronal loss appears with the aggregated form of τ protein, confirming that both pathological events occur before the formation of NFTs which contribute to the impairment of the disease [228].

τ protein is a substrate of GSK-3β, which activity results in its physiological phosphorylation of at least 36 different residues: for example Thr231, Tyr18, Ser199, Ser262, Ser396, Ser400, Ser404, and Ser416 that represent only a subset of over 70 phosphorylation sites identified in the whole τ structure [229]. The high-

est level of phosphorylated Thr231 (pThr-231) is detected in the temporal cortex in V/VI Braak stage, the last level of disease progression, while other phosphorylated residues such as Ser199 and Tyr18 are found in frontal cortex [229]. The phosphorylating action of GSK-3β requires the primed phosphorylation of different protein kinases [69].

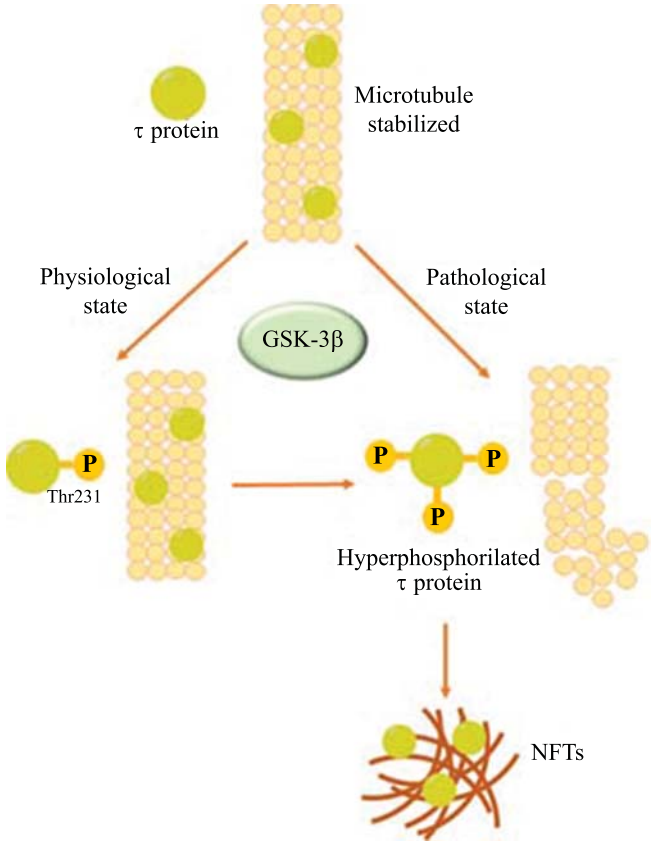


Fig. (5). τ protein stabilizes microtubules in a physiological situation. On the contrary, τ is hyperphosphorylated in pathological events resulting in a reduced possibility of binding microtubules. In this situation, the τ protein tends to self-assemble creating NFTs.

GSK-3β is involved in the phosphorylation of more possible sites on τ in comparison to GSK-3α; nevertheless, both two proteins have a crucial role in τ proteinopathy [230]. The phosphorylation is balanced by the action of protein phosphatases (PPs) that are expressed in several areas of the mammalian brain; the five PPs are PP1, PP2A, PP2B, PP2C and PP5 and, except for PP2C, they dephosphorylate τ protein in several phosphorylated sites [231]. Decreased levels of phosphatases are detected in AD-affected models [231]. CDK5 is known to act as a modulator of τ phosphorylation, and its overactivation in old AD transgenic mice revealed the loss of the CDK5-mediated inhibitory activity of GSK-3β. In fact, normally GSK-3β is inhibited by CDK5 through inhibition of PPs. Both PP1 and PPA2 have been reported to be able to activate GSK-3β. But in old AD transgenic mice regulation of GSK-3β activity is lost, highlighting GSK-3β as the target for therapeutic intervention [232, 233].

In AD brains, caspases, cysteine aspartate proteases, are found in an activated condition. It is demonstrated that τ protein is subjected to caspases-cleavage triggered by the aggregation of Aβ. Caspase 3 operates at the level of Asp421 while calpain-1 and caspase 6 at the level of the N-terminal domain in the τ protein [211, 234]. τ protein undergoes conformational changes triggered by the cleavage activity of caspases that determines its accumulation and aggregation into an insoluble and misfolding form leading to the formation of filaments and then NFTs [235]. Both caspase's activity and activation of GSK-3β lead to the development of AD [236]. In addition to the co-participation of both GSK-3β and caspases in the formation of τ aggregates, it should be noted that activated GSK-3β is involved in intrinsic apoptosis where activates caspases *via* mitochondrial death pathway [237]. In fact, together with its direct effect on τ protein, GSK-3β has the peculiarity to fit in several other interconnected signaling pathways. An example is the cooperation of GSK-3β with JNK *via* the Wnt-signaling pathway for the stabilization of microtubules, whose requirement is the concomitant inactivation of GSK-3β and activation of JNK [238].

Another opposite example is the GSK-3β-mediated regulation of the MARK-Par1 family protein (microtubule-associated regulating kinase, Partitioning defective 1), which is responsible to decrease the τ affinity towards microtubules, by phosphorylating the member MARK2 at Ser212, which leads to enzyme inactivation [239]. In addition to phosphorylation, GSK-3β is also involved in the impairment of clearance of both Aβ and τ aggregates. In particular, GSK-3β is able to phosphorylate some inhibitory sites of TSC2 (Tuberous Sclerosis Complex 2) determining the activation of mTOR and, as a consequence, the inhibition of autophagy that is an important biological process to remove toxic aggregates [203, 240].

Summarizing, GSK-3β is involved in several signaling pathways linked to AD: it is directly connected with the hyperphosphorylation of τ protein and the accumulation of Aβ plaques leading to the development of the initiating events of the pathology. Insights on its interconnections with other kinases signaling pathways are important to fully understand the multifaceted role of GSK-3β in Alzheimer's disorder.

4.2. Parkinson's Disease

PD is a neurodegenerative disorder with typical motor symptoms (bradykinesia, rigidity, postural instability, problems in coordination, and vocal cord paralysis) and it is characterized by injury in the dopaminergic system at the level of the *substantia nigra*. The hallmark of this disease is represented by the formation of Lewy Bodies (LBs) composed mainly of α-synuclein (α-Syn) [241-243]. α-Synuclein accumulation leads to an inhibition of tyrosine hydroxylase enzyme contributing to a decrease in dopamine biosynthesis [244]. Impairment and loss of dopaminergic neurons that control motor activity determine cell death and progression of the pathology, leading to decreased levels of dopamine and its biosynthesis [245-247]. In a physiological situation, dopamine homeostasis gets involved in neuroprotection: one of the dopamine byproducts is neuromelanin, a dark insoluble complex, that sequesters toxic molecules and metals. In oxidative stress and microglia activation in PD, neuromelanin is released in the extracellular environment contributing to worsening the disease [248]. Recently, Li and co-workers reported the effect of GSK-3β-mediated dopaminergic neuronal loss *in vivo* neurodegenerative models (mice treated with MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, the molecule that induces parkinsonism--like symptoms) [249]. Accordingly, the treatment of MPTP-mice with Tideglusib, an inhibitor of GSK-3β, showed neuroprotection, clearly demonstrating the implication of GSK-3β in Parkinson's disease [249]. GSK-3β plays an important role in phosphorylating α-synuclein, especially at Ser129, which in a pathological situation tends to self-assembly to produce insoluble oligomers that aggregate, and could form fibrils that cause neuronal toxicity, in this specific case the toxicity is directed towards dopaminergic neurons [250, 251]. GSK-3 is a downstream effector of the dopamine-activated signaling pathway of β-arrestin [252].

Dopamine receptors (DRs) are G protein-coupled receptors (GPCR), thus when they are activated, β-arrestin is recruited determining the classical clathrin-mediated endocytosis and the consequent receptor internalization and, according to Hwang and co-workers, the downregulation of DRs, paired with the altered levels of presynaptic dopamine, leads to a reduced transmission resulting in motor fluctuations in PD patients [253]. β-arrestin is involved also in G protein-independent signaling of GPCRs, with interaction with PP2A and Akt, determining the inactivation of Akt, thus activating GSK-3 (Fig. **6**) [249, 254-256]. In addition, NFTs are detected in both Alzheimer's and Parkinson's diseases [257]. τ protein, the major component of NFTs, is encoded by MAPT gene; this gene is discovered to be connected with AD as well as PD [258]. As in AD, GSK-3β plays an important role in phosphorylating τ protein even in PD [251, 259]. Kozikowski and co-workers have reported a series of malaimides that are able to inhibit the τ phosphorylation GSK-3β-mediated at Ser 396/404 resulting in a decrease of neurotoxicity in a cellular model of PD confirming that GSK-3β has an important role in the pathogenesis of PD [260].

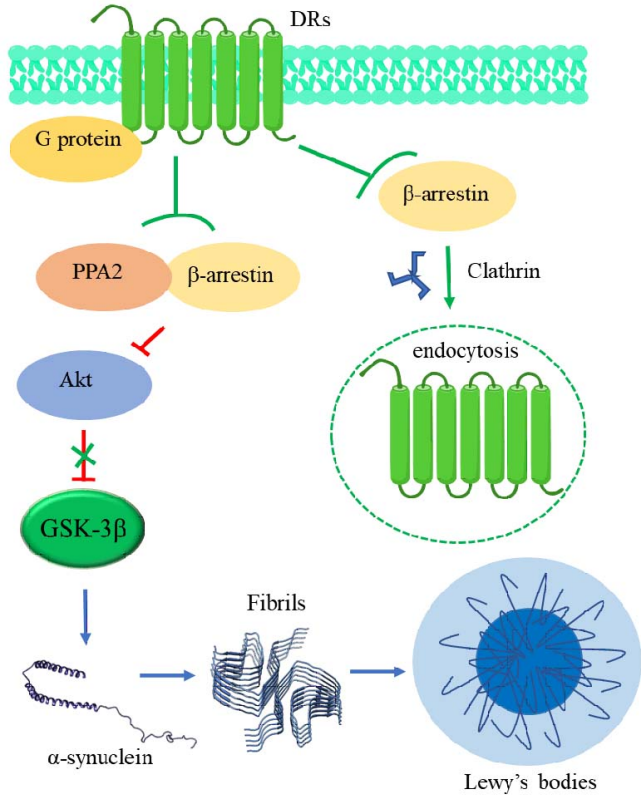


Fig. (6). β-arrestin signaling pathways in PD. When DRs are activated, β-arrestin is recruited determining the internalization of DRs *via* clathrin-mediated endocytosis. The G protein-independent signaling pathway involves the interaction between β-arrestin and PP2A and the consequent inactivation of Akt resulting in the activation of GSK-3β.

4.3. Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disease characterized by progressive loss and injury of motor neurons. The main pathogenic factor of this disorder is represented by mutations in TDP-43 (Trans activation response DNA binding protein 43). TDP-43 is principally localized in the nucleus, it binds both DNA and RNA, in

fact, it has a role in mRNA regulation at different steps [261-263]. In ALS, TDP-43 mislocalizes from the nucleus to the cytoplasm where it appears in an abnormal ubiquitylated, hyperphosphorylated, and N-terminally truncated form. The trigger point that determines the degeneration of motor neurons is the accumulation of this anomalous protein in the cytoplasm which creates aggregates within but also outside stress granulates (S-Gs), contributing to produce oxidative stress and neuronal toxicity (Fig. **6**) [264-270]. In fact, ubiquitylated and phosphorylated TDP-43 was detected in patient's ALS-affected brains [271]. Hyperubiquitylation and hyperphosphorylation are two posttranslational modifications that occur in TDP-43 in ALS models. Inclusion bodies are not completely composed of ubiquitylated TDP-43, this evidence suggests that this process can follow the phosphorylation one, even if both events can influence each other [271-273]. The phosphorylation of TDP-43 includes several residues such as Ser379, Ser403, Ser404, Ser409 and Ser410 [273]. The ubiquitin in a physiological situation determines the degradation of systems *via* proteosome as a positive role [274]. However, according to Fornai *et al.*, defects in the autophagy system are found in ALS models [275]. Lithium, a well-known GSK-3β inhibitor, can regulate the autophagy process by inducing it by decreasing IP3 (inositol-1,4,5-triphosphate) levels [276]. Interestingly, GSK-3β inhibition was found also to promote the cytoplasmic localization of TDP-43, but this was not linked to its incorporation in SGs nor with its hyperubiquitylation [277]. The abnormal form of TDP-43 determines a strong upregulation of GSK-3β [278]. The activation of this kinase in TDP-43 overexpressing systems causes the dysregulation of ER-mitochondria interactions, cellular calcium homeostasis and damages in organelles, a condition linked to neurodegenerative diseases [279, 280]. Dysregulation and changes in mitophagy, a type of autophagy, leading to problems in the elimination of damaged organelles, linked to the axonal transport that is injured in ALS [280, 281]. In a physiological state, the ER-mitochondria plays important roles in calcium and phospholipid exchanges and it is connected with the inflammatory response by constituting inflammasome [282, 283]. TDP-43 is linked to the dysregulation of ER-mitochondria functions, where GSK-3β activation has been associated with a decrease in the binding of VAPB (Vesicle-associated membrane protein-associated protein B/C) with PTPIP51 (Protein tyrosine phosphatase interacting protein 51) resulting in damage of ER-mitochondria and in alterations of its functions [284].

4.4. Frontotemporal *Dementia*

TDP-43 is one of the pathological hallmarks of frontotemporal dementia (FTD) as well as ALS. FTD is characterized by atrophy in the anterior temporal and frontal lobes and manifests itself with behavioral and cognitive deficits. Some of the patients affected by FTD display also a motor neuron disease (MND) and ALS is an MND-type disorder [271, 285]. As for ALS, FTD is featured by hyperphosphorylation and hyperubiquitylation of TDP-43 that tends to accumulate and to mislocalize at the level of cytoplasm, and the disruption of ER-mitochondria in which GSK-3β plays an important role [284, 286]. In 10% of patients affected by FTD, it is discovered a mutation of the gene encoding for the τ protein, that leads protein aggregates which form fibrils, hence the role of GSK-3β becomes more clear as it phosphorylates τ in tauopathies [287].

4.5. Huntington's Disease

HD is an autosomal dominant disease featured by cognitive and behavioral impairments and by the appearance of involuntary movements [288]. The disorder is characterized by an expansion of the tripeptide CAG in the HTT gene. HTT encodes for Huntingtin (Htt) protein that contains in its N-terminal domain a polyglutamine (PoliQ) segment. This protein is arranged in a structure containing an ordered pattern of repeats with the name of HEAT (Huntingtin, Elongation factor 3, Protein phosphatase 2A, and TOR1); changes in this cluster determine posttranslational modifications for example glycosylation, phosphorylation and cleavage by caspases and calpains [289, 290]. The mutant form of Htt contains the PoliQ segment of an aberrant length that promotes protein misfolding and aggregation resulting in neurotoxicity and neurodegeneration. Mutant Htt was found to accumulate in inclusion bodies (IBs) in several brain areas such as *striatum*, *cerebellum*, and spinal cord [291]. During the aggregation process, several crucial proteins could be sequestered from the environment, such as transcription factors and proteasomes, resulting in alterations in both transcription and proteasome activity [291]. Despite different and conflicting evidences are provided for the role of GSK-3β in HD, its interconnection in several signaling pathways and biological aspects is demonstrated towards the increase in GSK-3β expression and action in *hippocampus* in HD's mouse model [240, 292, 293]. According to Fernandez-Nogales *et al.*, the inhibition of GSK-3β in different types of cells and animal HD's models seems to protect against cell death triggered by the aberrant form of PoliQ and the aggregation of Htt [294]. In support of these experimental evidences, Akt-mediated phosphorylation at Ser-421

residue in Htt was found to give neuroprotection inhibiting the toxicity induced by the mutant Htt as also the accumulation of PoliQ inclusions. In addition, in samples from HD patients were found high concentrations of an inactivated truncated fragment of Akt [295]. As a consequence, if Akt is inactive, the levels of activated GSK-3β increase [295, 296]. On the contrary, Gines *et al*. assumed that there is an Akt activation in HD's *striatum* cell model by detecting increased levels of $Ser(P)^{473}$-Akt that is one of the two well-known activatory phosphorylation residues: triggering GSK-3β inactivation [292, 293]. This suggests that there are several complicated and interconnected mechanisms at stake. In support of the negative role of GSK-3β, there is evidence on the accumulation of hyperphosphorylated τ protein in HD that, together with caspase 3 activation, is a common feature of AD [297, 298]. Another event, previously mentioned in AD, is the autophagy process that plays an important role also in HD [299]. Another characteristic observed in HD is the alteration in lipids homeostasis on the membrane and, in particular, alterations in cholesterol levels were found in HD's patients and in HD *in vivo* models [300, 301]. Htt is a membrane-associated protein involved in vesicle membrane trafficking and mutant Htt exhibited a stronger association with membranes. In particular, in HD an altered biosynthesis of sterols, an accumulation of cholesterol, and an increment of lipid rafts, membrane domains important in signaling transduction, were detected [302]. Active GSK-3β is recruited at the level of lipid rafts, where it controls and modifies several transcription factors that regulate neuronal functions. Inhibition of GSK-3β determines an increase in neuronal survival by reducing the cholesterol amount and accumulation [303].

4.6. Other Neurodegenerative and Neuroinflammatory Diseases

GSK-3 is also involved in other types of neurodegenerative/neuroinflammatory diseases. Its engagement is known for tauopathies: Alzheimer's disease as well as Pick's disease (PiD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) by hyperphosphorylating τ protein [304, 305]. Lesser-known is the role of GSK-3 in Batten Disease that is characterized by neurodegeneration induced by the lack of cathepsin D, a lysosomal protease important for autophagic activity: the precise trigger event is unknown but Walls *et al.* assume that a dysregulation of PI3K/Akt signaling pathway that regulates apoptosis and autophagic stress can be involved. The inhibition of GSK-3β as a consequence of the activation of Akt can lead to the accumulation of autophagosomes [306]. Dysregulation of the same signaling pathway, as well as the activation of caspase 12, are detected also in Prion diseases, transmissible spongiform encephalopathies (TSEs), that comprise Creutzfeldt–Jakob disease. According to *in vitro* and *in vivo* experiments, the recruitment of cellular Prion Proteins in an abnormal and aggregated form induces neurotoxicity through the hyperactivation of Akt signaling pathway and correlated inhibition of GSK-3β [307].

The evidence collected on the multiple roles of this protein kinase in several neurodegenerative diseases make it an appealing target for future therapeutic developments.

5. GSK-3β INHIBITORS

The key role played by GSK-3β in multiple biochemical pathways in the cell has made this kinase an attractive target for the development of novel pharmacological agents capable of selective inhibition to verify its potential as an effective target in the treatment of a variety of diseases and to better understand its mechanism and regulation processes. Among the GSK-3β inhibitors, small cations and several organic compounds, both of natural and synthetic origin, have been developed and investigated. Inhibition can be accomplished by several mechanisms and consequently, can be classified in: (*i*) inhibition by metals, (*ii*) ATP-competitive inhibition, (*iii*) non-ATP competitive inhibition, (*iv*) multitarget inhibition.

In the next section GSK-3β inhibitors under clinical trials will be discussed.

5.1. GSK-3β Inhibitors in Clinical Trials

Despite a very large number of inhibitors of GSK-3β that have been identified during the last two decades, only a few of them have reached clinical trials: AZD1080, LY2090314, Tideglusib (NP-031112), 9-ING-41, and TSW119 (Fig. **7**).

The indolyl derivative AZD1080 (**1**) was synthesized by AstraZeneca and it is a potent ATP-competitive inhibitor of GSK-3α/β [K_i (GSK-3α) = 6.9 nM, K_i (GSK-3β) = 31 nM], that shows >14-fold selectivity towards CDK2, CDK5, CDK1 and extracellular signal-regulated kinase 2 (ERK2). It is bioavailable after oral administration and able to pass the BBB [308]. *in vitro*, AZD1080 (**1**) inhibits the phosphorylation of τ both in human cells expressing the protein and in intact rat brains. Interestingly, subchronic but not acute administration of AZD1080 (**1**) reverses the block of LTP caused by MK-801, a non-competitive NMDA receptor antagonist, demonstrating that prolonged

GSK-3 inhibition is required to restore synaptic plasticity [308]. In 2006, **1** has entered clinical Phase I: oral administration of AZD1080 (**1**) in ascending doses to healthy volunteers confirmed the preclinical data. However, clinical trials have been abandoned due to the chronic cholecystitis observed in the dog at clinically relevant doses in preclinical studies [309].

The maleimide derivative LY2090314 (**2**) reached clinical trials for cancer treatment. LY2090314 (**2**), developed by Eli Lilly, is a potent reversible ATP-competitive inhibitor with IC_{50} values of 1.5 nM and 0.9 nM for GSK-3α and GSK-3β, respectively, which is able to stabilize β-catenin, *in vitro*.

A Phase I study has been conducted to test LY2090314 (**2**) in combination with pemetrexed and carboplatin in patients with advanced/metastatic cancer, including mesothelioma, non-small cell lung carcinoma (NSCLC), and breast cancer [310], and in Phase I/II LY2090314 (**2**) was tested in combination with Gemcitabine and FOLFOX (leucovorin + 5-fluorouracil + oxaliplatin) in patients with metastatic pancreatic cancer [311]. A Phase II trial on patients with refractory/relapsed or untreated acute myeloid leukemia (AML) revealed a weak action, and therefore a limited clinical benefit, of **2** as a single agent [312, 313].

Tideglusib (NP-031112, **3**) is an orally available, BBB permeable, small-molecule drug of the thiadiazolidinone class, developed by Neuropharma. It is a non-ATP competitive GSK-3β inhibitor with IC_{50} of 60 nM, whose mechanism of action has been investigated [314, 315]. Dominguez *et al.* demonstrated an irreversible behavior, reporting the lack of recovery in enzyme function after the unbound drug has been removed from the reaction medium and a dissociation rate constant not significantly different from zero. Moreover, Tideglusib (**3**) failed to inhibit other kinases containing a residue homologous to Cys199 in their active site, which means that it acts through a specific inhibition mechanism. Nevertheless, a covalent modification of GSK-3β by Tideglusib (**3**) is not confirmed, but the irreversible inhibition and the slow turnover of GSK-3β in neuronal cells can prolong the duration of the pharmacological effect and can be exploited to maximize its therapeutic potential [316]. *in vitro*, Tideglusib (**3**) reduces τ phosphorylation and prevents apoptotic death in human neuroblastoma cells and murine primary neurons. Moreover, it exerts a potent neuroprotective effect from glutamate-induced toxicity on rat primary astrocytes or microglial cultures (decrease of TNF-α and COX-2 expression and of apoptotic cells). In adult male rats, Tideglusib (**3**) injected into the hippocampus dramatically reduces kainic acid-induced inflammation, while in APP/τ double transgenic mice, lowers the levels of τ phosphorylation, decreases amyloid deposition and plaque-associated astrocytic proliferation and prevents memory deficits [317, 318].

Tideglusib has also been proposed as a potential agent for natural tooth repair since the canonical Wnt/β-catenin signaling pathway is crucial for reparative dentinogenesis following tooth damage [319, 320].

Tideglusib (**3**) reached clinical trials Phase II for the treatment of AD [321], autism spectrum disorders (ASD) [322], PSP and myotonic dystrophy. In a first pilot clinical study on patients with AD [321], Tideglusib (**3**) showed a satisfactory safety profile and significant improvement in cognition compared with placebo-treated patients [323]. In a larger Phase II study [324], despite confirming its safety and tolerability, no significant cognitive improvements in the patients were observed [325]. The treatment of patients with mild to moderate PSP in Phase II clinical trial assessed drug safety but did not show any clinically significant improvement [326, 327]. In a Phase II study, Tideglusib was evaluated for the treatment of adolescent, and adult congenital and juvenile-onset type 1 myotonic dystrophy [328]. The drug was well tolerated and the patients showed an improvement of the PSP symptomatology at neuromuscular and cognitive levels [329]. After Phase II studies assessed the safety and efficacy of Tideglusib (**3**), a clinical Phase II/III trial is recruiting patients aged 6 to 16 years diagnosed with Congenital Myotonic Dystrophy (Congenital DM1) and the study completion is expected in 2022 [330].

9-ING-41 (**4**), a maleimide-based ATP-competitive small molecule GSK-3β inhibitor, has shown more selectivity for GSK-3β than for other related kinases [331]. The antitumor activity of 9-ING-41 (**4**) has been revealed in cancer cell lines studies and in animal models in several tumors: neuroblastoma [332], glioblastoma [333], breast cancer [334], ovarian cancer [335], B-cell lymphoma [336], bladder cancer [337], and renal cancer [338, 339]. 9-ING-41 (**4**) attenuates the progression of pulmonary fibrosis by improving lung function and inhibiting myofibroblast differentiation both *ex vivo* and *in vivo* [340]. Currently, 9-ING-41 (**4**) is under Phase I or II clinical trials in patients with refractory advanced cancer, sarcoma, advanced metastatic salivary gland carcinoma, myelofibrosis and in pediatric patients with refractory malignancies [341]. Preliminary results of Phase I in oncologic patients with refractory tumors indicate that 9-ING-41 (**4**) is well tolerated with significant antitumor activity as monotherapy and combined with chemotherapy. A biologically active dose has been determined, but the maximum tolerated dose (MTD) has not been determined [342].

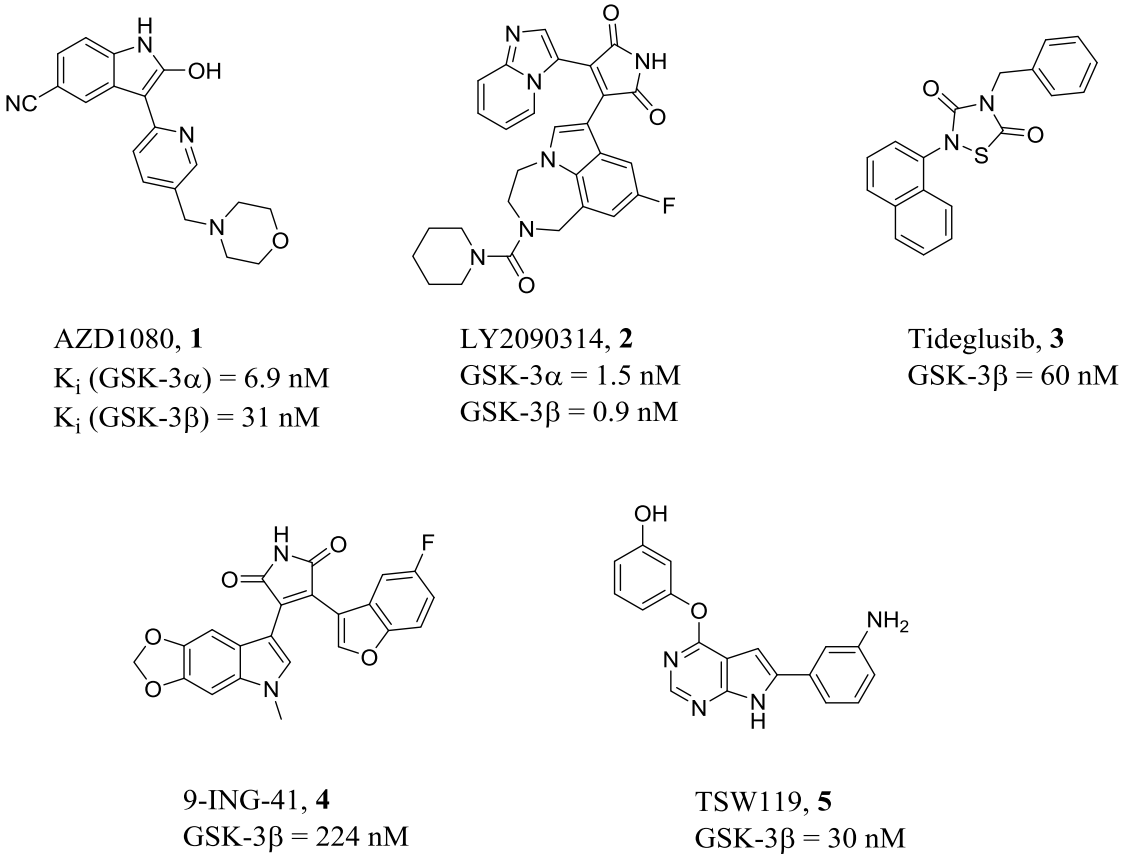


Fig. (7). GSK-3β inhibitors that reached clinical trials (**1**-**5**). If not specified, the reported data are IC_{50} values.

Among the ATP-competitive GSK-3β inhibitors, a heteroaromatic bicyclic core proved to be a suitable scaffold for obtaining the potent GSK-3β inhibitor TWS119 (**5**), a 4,6-disubstituted pyrrolopyrimidine. This synthetic small molecule was identified in 2003 by Schultz and coworkers through a high-throughput phenotypic cellular screen for compounds capable to induce neuronal differentiation of pluripotent mouse embryonic stem cells (ESC) [343]. TWS119 inhibited GSK-3β with an IC_{50} of 30 nM. The inhibition of GSK-3β induces Wnt/β-catenin signaling, thus arresting CD8+ T cell differentiation into effector cells and promoting the generation of self-renewing, multipotent CD8+ memory stem cells, or T memory stem cells (T_{SCM} cells), endowed with proliferative and antitumor capacities [344]. Recently, Gattinoni and co-workers described a protocol to generate a relevant number of clinical-grade tumor-redirected T_{SCM} by activating *naive* T cell precursors in the presence of IL-7, IL-21, and TWS119 (**5**), and, by genetically engineering methods, they expressed a CD19-specific chimeric antigen receptor (CD19-CAR) [345]. Currently, a Phase I trial is evaluating the activity of CD19-CAR–modified CD8+ T_{SCM} cells in patients with B-cell malignancies refractory to prior allogeneic hematopoietic stem cell transplantation (alloHSCT) and assessing the safety and effectiveness of their administration to patients [346]. In animal models, TWS119 (**5**) is effective in reducing stroke-related brain damage through activation of the Wnt/β-catenin signaling pathway [100, 347]. Since the osteogenic differentiation of bone mesenchymal stem cells (BMSCs) is improved *via* the activation of the Wnt/β-catenin pathway, a nanohybrid scaffold of carbonated hydroxyapatite/chitosan (CHA/CS) loaded with TWS119 (**5**) was fabricated with the aim of enhancing the osteogenic differentiation of BMSCs through the controlled release of TWS119 (**5**). The construct was tested both *in vitro* in BMSCs and *in vivo* in rat cranial defect models and exhibited excellent biocompatibility and drug delivery properties, and prominent capacity in promoting the osteogenesis differentiation of BMSCs [348].

5.2. Inhibition by Metal Ions

Since a magnesium ion is required for the binding of ATP into the catalytic pocket of GSK-3β, the competition with this cation can be exploited to obtain an inhibitory effect.

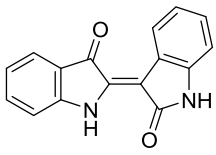
GSK-3β is inhibited by lithium not only directly by competing with Mg^{2+}, but also indirectly by increasing the inhibitory N-terminal serine phosphorylation [349]. Lithium salts treatment of acute mania was described more than 70 years ago [350] and represents the mainstay treatment for bipolar disorder through inhibiting inositol monophosphatase. Moreover, the inhibition of GSK-3 has been related to the mood-stabilizing behavioral aspects of lithium action [351]. A recent study outlined the potential of lithium treatment in obsessive-compulsive disorder (OCD), a disease where the overactivity of GSK-3β is consistent with a downregulation of the Wnt pathway. Mutant murine models of OCD presented increased GSK-3β activity [352]. Lithium down-regulates two central processes in the pathogenesis of AD, preventing hyperphosphorylation of microtubule-associated τ protein and the induction of neuronal death mediated by overproduction of the A*β* peptide both in the cell and *in vivo* models of AD, and improves cognitive function in transgenic mice [353]. Several clinical trials have proved the efficacy of lithium in AD; long-term treatment with lithium in patients with mild cognitive impairment (MCI), a high-risk condition for the progression of AD, improved global cognitive function, which was associated with significantly reduced concentrations of phosphorylated τ in cerebrospinal fluid (CSF) [354]. However, other clinical studies have found no evidence of lithium's ability to prevent dementia, ameliorate cognition, and reduce tau phosphorylation [317]. In a recent study [355], patients with AD were treated with microdoses (300 μg per day) for 15 months and a slowing of cognitive decline was observed *vs* placebo-treated patients. Recently, a clinical Phase I study was performed to establish the minimum dose of lithium capable to block GSK-3 in patients with MCI, and no serious adverse events were reported even at the highest dose [356]. Currently, a clinical Phase IV study is recruiting to assess whether lithium has a role as an anti-dementia agent in elderly patients with MCI that are at risk of becoming demented [357] and another Phase I clinical trial is recruiting to assess the effects of lithium among PD patients [358]. These studies confirm the interest in the efficacy of lithium in neurodegenerative diseases, although the need to investigate its mechanism of action is of utmost importance.

Other metal ions such as beryllium, mercury, copper and zinc are capable of GSK-3 inhibition [359, 360], and, showing IC_{50} in the micromolar concentration range, they are more potent than lithium, whose IC_{50} is in the millimolar concentration range. Unlike lithium, zinc ion is naturally present in cells as a cofactor of many enzymatic systems. Zinc inhibits GSK-3 with an IC_{50} =15 μM and elevates cellular β-catenin levels [359]. Zinc deficiency in the body is related to major depression, as outlined by several studies in animal models [361, 362], and symptoms are alleviated by zinc administration [361]. Low zinc level in patients with major depression has often been detected and the symptomatology is improved with supplementary zinc through diet [363, 364]. However, at the present state of knowledge, it is not possible to correlate the therapeutic activity of zinc in cognitive diseases with its capacity to inhibit GSK-3.

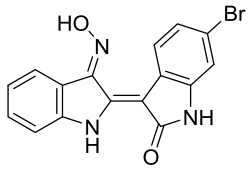
5.3. ATP-Competitive Inhibitors

5.3.1. Natural Origin ATP-Competitive Inhibitors and Structurally Derived Compounds

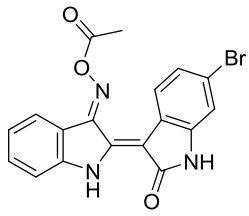
Indeed, the natural environment is a source of organic structures with promising biological activities for CNS diseases and several GSK-3 inhibitors were isolated both from marine organisms and plants (Figs. **8** and **9**). Indirubin (**6**), which is a bis-indole alkaloid found in some terrestrial plants and sea shells, is a purple dye used in traditional Chinese medicine able to inhibit CDKs and GSK-3β at nanomolar levels. In the years, several analogues were synthesized, all capable to inhibit both GSK-3β and CDKs in an ATP-competitive manner. Among all, the most interesting analogue is 6-bromoindirubin-3'-oxime (6-BIO, **7**), which has demonstrated higher selectivity for GSK-3β than for CDKs (16-fold). A limiting factor for this compound is its poor solubility in water, which is reflected in non-reproducible biological results. To improve the solubility in water, several 6-BIO analogues bearing a polar or ionizable chain on the oxymic moiety have been synthesized, which will be discussed later [365]. 6-BIO (**7**) has been tested in different neuronal systems, demonstrating neuroprotective effects against kainic acid- and MPTP-induced neuronal death and amelioration of many AD symptoms, including τ hyperphosphorylation and Aβ accumulation [313, 317]. In addition, it has shown anti-convulsant activity in Zebrafish and mouse models and promotes the differentiation of human embryonic stem cells (HESCs) or human-induced pluripotent stem cells (HIPSCs) to hepatocyte-like cells and cardiomyocytes, respectively [366, 367]. There are evidences that periodontal ligament stem cells (PDLSCs) may play an important role in the regeneration of periodontal tissues [368]. Since the osteogenic differentiation of PDLSCs can be regulated by



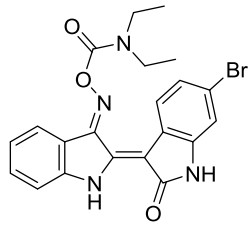
Indirubin, **6**
GSK-3β = 5-50 nM



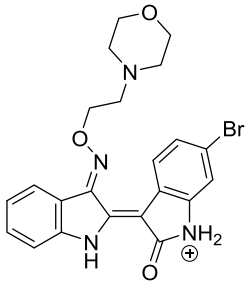
6-BIO, **7**
GSK-3β = 5 nM
5-LO = 0.2 μM



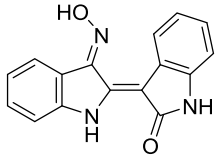
6-BIO-acetoxime, **8**
GSK-3 = 10 nM



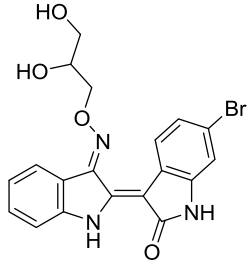
6-BIDECO, **9**
GSK-3 = 30 nM



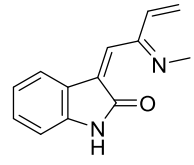
6-BIMYEO, **10**
GSK-3 = 0.11 μM



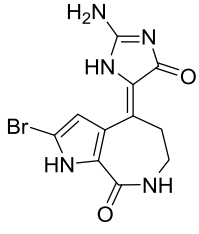
I3MO, **11**
GSK-3β = 22 nM
CDK1 = 180 nM
CDK5 = 100 nM



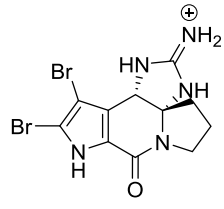
6-BIGOE, **12**
GSK-3 = 34 nM



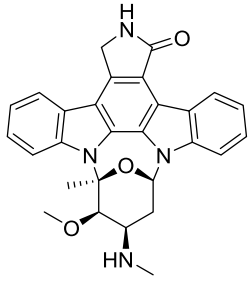
13
GSK-3β = 4.19 nM



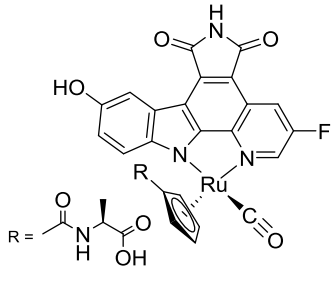
Hymenialdisine, **14**
GSK-3β = 10 nM
CK-1 = 35 nM
CDK-1 = 22 nM
CDK-5 = 28 nM



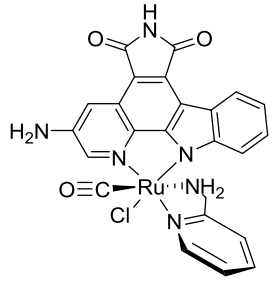
Dibromocantharelline**, 15**
GSK-3β = 3 μM



Staurosporine**, 16**
GSK-3 = 15 nM



(R_{Ru})-NP549, **17**
GSK-3β < 0.04 nM



Λ-OS1, **18**
GSK-3α = 0.9 nM
GSK-3β = 6 nM

Fig. (8). GSK-3 ATP-competitive inhibitors from natural sources and structurally derived inhibitors (**6-18**). Reported data are IC_{50} values.

the Wnt pathway, a hybrid system composed of a hyaluronic acid (HA) hydrogel embedded with 6-BIO-encapsulated poly(lactic-*co*- glycolic acid) (PLGA) microspheres was developed [369]. PLGA-BIO−HA hydrogel system was tested *in vivo* in a mouse periodontitis model, and the experiments showed that it promotes the proliferation, migration, and osteogenic differentiation of PDLSCs, enhancing the gene expression of osteogenic markers and alveolar bone regeneration [369].

Recently, the potential cytoprotective activity of 6-BIO (**7**) in normal human cell senescence was investigated. *in vitro* experiments in human diploid skin fibroblasts, 6-BIO (**7**) reduced the oxidative load, conferred protection against oxidative stress-mediated DNA damage, and it also activated antioxidant responses and proteostasis network (PN). 6-BIO (**7**)-mediated GSK-3 inhibition leads to stabilization, nuclear localization, and transcriptional activation of NRF2, a key transcription factor regulating the expression of a wide range of phase II and antioxidant enzymes [370]. Recently, the cardiac anti-aging effect of 6-BIO (**7**), *via* interaction with either GSK-3β or mTOR, was outlined in a ventricular myoblast cell line, suggesting that 6-BIO (**7**) might play a role in the prevention of cardiovascular diseases [371].

A strictly related derivative of 6-BIO (**7**) is 6-BIO-acetoxime (6-bromoindirubin acetoxime) (**8**) (Fig. **8**), a potent dual GSK-3α/β inhibitor with IC_{50} of 10 nM, with a selectivity more than 240-fold over CDK5/p25, CDK2/cyclin A and CDK1/cyclin B. Recently, 6-BIO-acetoxime (**8**) was tested *in vivo* in animal models, revealing anticonvulsant action through GSK-3 inhibition, thereby suggesting GSK-3 as a potential therapeutic target for epilepsy [372]. Furthermore, it was found to reduce the invasiveness of gliomas, primarily through activating apoptosis [373].

Among 6-BIO derivatives, it is worth to cite 6-BIDECO (6-bromoindirubin-3-[O-(*N,N*-diethylcarbamyl)-oxime] (**9**) and 6-BIMYEO (6-bromoindirubin-3-[O-(2-morpholin-1-ylethyl)-oxime] hydrochloride) (**10**), both exhibiting higher selectivity towards GSK-3 compared with other τ kinases (for 6-BIDECO, IC_{50} = 0.03 μM for GSK-3, >10 μM for CDK1, and 10 μM for CDK5; for 6-BIMYEO, IC_{50} = 0.11 μM for GSK-3, 1.8 μM for CDK1, and 0.9 μM for CDK5). 6-BIDECO (**9**) and 6-BIMYEO (**10**) are not neurotoxic and potently reverse τ phosphorylation and apoptosis induced by okadaic acid (OKA) in cultured neurons [374]. Other derivatives of interest are indibubin-3'oxime (I3MO, **11**) and 6-bromoindirubin-3′-glycerol oxime (6BIGOE, **12**) (Fig. **8**), two highly potent GSK-3 inhibitors in cell-free kinase assays with IC_{50} values of 22 and 34 nM, respectively [375], endowed with kinase selectivity and intracellular availability. Some indirubine derivatives have been proposed as dual inhibitors. In particular, I3MO (**11**) proved to be able to inhibit GSK-3β, CDK1, and CDK5 in the nanomolar range. Both cyclin-dependent kinase and GSK-3β activities are increased in the brain of AD patients [376]. For this reason, the use of dual GSK-3β/CDK inhibitors could represent an attractive approach for the treatment of neurodegenerative disorders [377]. I3MO (**11**) showed to decrease several AD--like phenotypes and to attenuate memory deficits in a mouse AD model [376].

In particular, 6BIGOE (**12**) exerts potent anti-inflammatory activities, suppressing the release of proinflammatory cytokines and COX-2-derived prostaglandines and elevating anti-inflammatory IL-10, thus possessing promising therapeutic potential in inflammation-related diseases [375].

By combining the structural features of 6-BIO (**7**) and SU9516, a selective CDK-2 inhibitor, a potent 2-oxindole GSK-3β inhibitor with an IC_{50} value of 4.19 nM was developed (**13**) [378]. Docking studies suggested that **13** occupies the hydrophobic cleft of the allosteric binding site, establishing a hydrogen bond between NH and Asp133 backbone, characteristic of allosteric GSK-3β inhibitors [379].

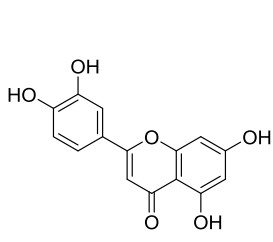
Originally isolated from marine sponges *Axinella verrucosa*, *Acantella aurantiaca*, and *Hymeniacidon aldis,* hymenialdisine (**14**), an oridoid alkaloid, has been identified as a potent, non-selective ATP-competitive inhibitor of different kinases, including GSK-3β (IC_{50}=10 nM) and CK-1 (IC_{50}=35 nM) [380]. Hymenialdisine (**14**) was first isolated for its anti-inflammatory properties, possibly due to inhibition of GSK-3β in the NF-κB pathway. Moreover, it demonstrated the ability to inhibit τ phosphorylation *in vivo* at sites that are hyperphosphorylated by GSK-3β in AD [381]. Recently, hymenialdisine and its derivatives have been reviewed by Nanduri and coworkers [382]. Another sponge metabolite, dibromocantharelline (**15**), showed moderate inhibition of GSK-3β with an IC_{50} value of 3 μM, but no inhibition on CDK1 and CDK5 [383]. Based on these findings, dibromocantharelline (**15**) could be considered as a natural template for the development of semi-synthetic selective GSK-3β inhibitors.

Among the derivatives reported in the literature, there is staurosporine (**16**), an alkaloid isolated from the bacterium *Streptomyces staurosporeus*, well known for its antimicrobial, hypotensive and cytotoxic properties, that inhibits GSK-3β at nanomolar level

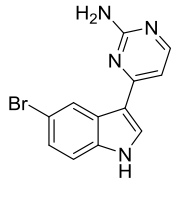
(IC_{50} = 15 nM). The lack of specificity has precluded its clinical use but has made it a valuable research tool. In fact, staurosporine has been the ancestor of a series of maleimide derivatives developed over the years [384]. *N*-heterocyclic ruthenium complexes acting as protein kinase inhibitors were first reported by Meggers *et al.* [385]. Ru(II)-complexes capable of inhibiting GSK-3 were developed starting from staurosporine (**16**). This strategy led to the discovery of a potent arene ruthenium complex (R_{Ru})-NP549 (**17**) (Fig. **8**), an ATP-competitive GSK-3β inhibitor which exhibited an $IC_{50} \leq 0.04$ nM [24]. The close structural resemblance of (R_{Ru})-NP549 (**17**) with staurosporine (**16**) allows a similar binding mode within the ATP-binding site, and the Ru(II)-coordination sphere can be opportunely modified to maximize the binding interactions [386]. Among Ru(II)-based inhibitors, another example is Λ-OS1 (**18**), a non-selective octasporine derivative able to inhibit both GSK-3α and GSK-3β at nanomolar concentration [33].

Recently, the citrus flavonoid luteolin (**19**) (Fig. **9**) has been reported as a micromolar GSK-3β inhibitor [387]. **19** was initially known to be a potent free radical scavenger, anti-inflammatory agent, immunomodulator and, in particular, it seems to have a potential role in colorectal cancer therapy, through interaction with the Wnt pathway. GSK-3β inhibition by luteolin (**19**) also resulted in a decrease of soluble Aβ levels and promotes the association between PS-1 and APP, both *in vitro* and *in vivo* [388].

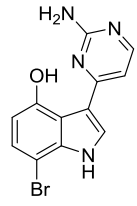
Meridianins, brominated 3-(2-aminopyrimidine)-indoles isolated from the tunicate *Aplidiummeridianum*, inhibit various protein kinases such as CDK, GSK-3, PKA, and CK1. Among the most interesting, Meridianin C (**20**) and Meridianin E (**21**) (Fig. **9**) were found to be good inhibitors of GSK-3β and showed promising antitumor activities [389, 390]. Meridianin C analog **22** (Fig. **9**) demonstrated a GSK-3β inhibitory activity in the micromolar concentration range (IC_{50} = 5.85 μM) and showed a much higher glucose uptake than Meridianin C with no significant toxicity against HepG2 cells [391].



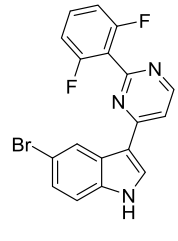
Luteolin, **19**
GSK-3β = 1.5 μM



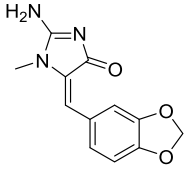
Meridianin C, **20**
GSK-3β = 0.5 μM
CDK1/cyclin B = 3.0 μM
CDK5/p25 = 6.0 μM



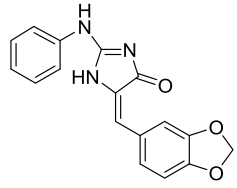
Meridianin E, **21**
GSK-3α = 0.9 μM
GSK-3β = 2.5 μM
CDK1/cyclin B = 0.18 μM
CDK5/p25 = 0.15 μM
CK1 = 0.40 μM



22
GSK-3β = 5.85 μM

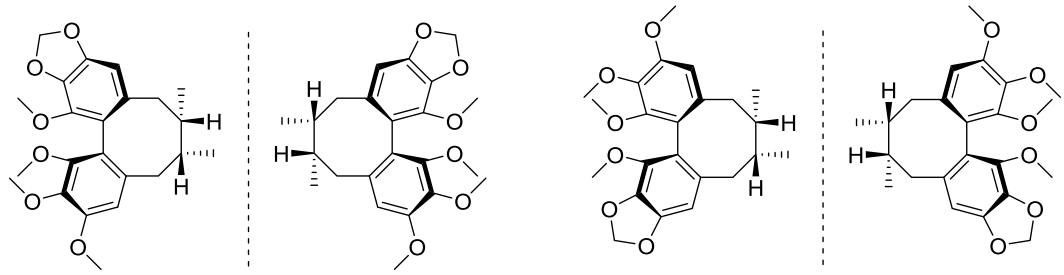


Leucettamine B, **23**
GSK-3β = 15 μM



Leucettine L41, **24**
GSK-3α = 0.21 μM
GSK-3β = 0.38 μM

Fig. (9). GSK-3 ATP-competitive inhibitors from natural sources and structurally derived inhibitors **(19-24**). Reported data are IC_{50} values.



(+)-**25**
GSK-3β = 0.341 μM

(-)-**25**
GSK-3β = 0.291 μM

(+)-**26**
GSK-3β = 0.081 μM

(-)-**26**
GSK-3β = 0.073 μM

Fig. (10). Stereoisomers of Schisandrin B [399]. Reported data are IC_{50} values.

Among marine natural products, it is worth to mention the alkaloid Leucettamine B (**23**), which displayed an IC_{50} value of 15 μM for GSK-3 and IC_{50}s in the submicromolar/micromolar range for DYRK1A, DYRK2, CLK1, and CLK3 [392, 393]. Optimization of the leucettamine scaffold leads to a new series of derivatives, Leucettines, a family of pharmacological inhibitors for the potential development of novel AD therapeutic agents [393]. In particular, Leucettine L41 (**24**) inhibits GSK-3α and GSK-3β with IC_{50} values of 0.21 and 0.38 μM, respectively, and interacts very specifically with kinases involved at different levels in the onset and development of AD, such as then above mentioned DYRKs and CLKs, as well as PIM1, CK2, and the lipid kinase PIKfyve [39].

Schisandrin B (**25, 26**), a dibenzocyclooctadiene lignan, is the main active component of *Schisandra chinensis*, a herb commonly used in treating mental illness and memory loss in traditional Chinese medicine. This compound possesses anti-AD effects in A*β*-induced dementia in an animal model [394], along with other biological effects, including antioxidant [395], anti-inflammation [396], and neuroprotective activity [397]. Evidence of low toxicity and the ability of crossing the BBB make Schisandrin B (**25,26**) a potential lead compound for AD treatment. However, the main issue is Schisandrin B is a mixture of several stereoisomers (**25,26**) [398], which makes it difficult to interpret the results of *in vivo* and *in vitro* studies. Recently, four stereoisomers of Schisandrin B have been isolated, fully characterized ((+/-) **25**, (+/-) **26**, Fig. **10**), and evaluated as GSK-3β inhibitors. In particular, stereoisomers (+)-**26** and (−)-**26** were found to be ATP-competitive GSK-3β selective inhibitors with IC_{50} in the nanomolar range, ((+)-**25** IC_{50} = 0.341 μM, (−)-**25** IC_{50} = 0.291 μM, (+)-**26** IC_{50} = 0.081 μM, (−)-**26** IC_{50} = 0.073 μM), and with efficacy in modulation of the p-GSK-3β/τ pathway and glycogen hepatic level both *in vitro* and *in vivo* [399].

All the reported results suggest that the discovery of novel scaffolds from natural sources is still an open field and could provide promising therapeutic candidates to be investigated for the treatment of neurodegenerative disorders. Synthetic analogs of natural compounds can provide a more detailed SAR profile to improve both pharmacodynamic and pharmacokinetic profiles.

5.3.2. Synthetic ATP-Competitive Inhibitors

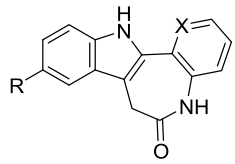
Among the first synthetic GSK-3 inhibitors reported (Fig. **11**) were the 7,12-dihydro-indolo[3,2-*d*]benzazepin-6(5*H*)-ones (paullones), fused tetracyclic compounds that inhibit GSK-3 within the nanomolar concentration range but also some CDKs. Paullones were initially identified by a screening of compounds in the National Cancer Institute collection, which aim to the identification of compounds that could act as CDK inhibitors, using the COMPARE algorithm [400], and the CDK inhibitor flavopiridol as a reference [401]. Kenpaullone (**27**), alsterpaullone (**28**), and the aza analogs azakenpaullone (**29**) and cazpaullone (**30**) showed IC_{50} values within the nanomolar range and are widely used in various experimental settings as GSK-3 inhibitors [402]. It has been reported that compound **27** reduces the production of Aβ in cells overexpressing APP [403] and promotes cell differentiation of dopaminergic neurons, a useful feature in PD treatment [404]. Instead, treatment with the derivative **28** seems to prevent τ phosphorylation [405, 406] and to block NMDA-induced LTD in cell cultures [407], while both compounds present neuroprotective properties against various kinds of stress. Moreover, **28** slowed down the

degradation of survival motor neuron (SMN) protein in spinal muscular atrophy (SMA) human fibroblasts, supporting the use of GSK-3 inhibitors in treatment of SMA [408]. Cazpaullone **30** was found to exhibit potent and selective GSK-3β inhibitory activity (IC_{50} = 8 nM), to promote β-cell protection and replication, and to protect from induced stress [409].

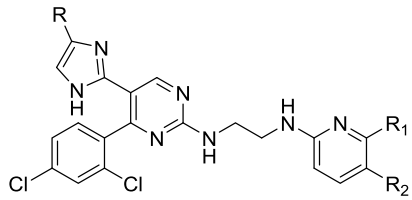
In the early 2000s, Chiron developed a series of purine analogs with an aminopyrimidine scaffold that inhibit GSK-3 within the nanomolar concentration range [410]. The potent inhibitors CHIR98014 (**31**), CHIR99021 (**32**), and CT20026 (**33**) were initially investigated for the treatment of diabetes: oral treatment for 30 days with CT20026 (**33**) reduced the disease progression in Zucker diabetic fatty (ZDF) rats [411], and the evaluation of CHIR98014 (**31**) and CHIR99021 (**32**) in rodent models of type 2 diabetes revealed that single oral doses lowered hyperglycemia within 60 min, enhanced insulin-stimulated glucose transport, and improved glucose disposal without increasing insulin levels [49]. Later, CHIRs have been tested in neuronal systems: GSK-3β inhibition led to a reduction of τ phosphorylation, arrest of NMDA-mediated LTD, and maintenance of pluripotency in mouse cells, through activation of the Wnt pathway [407, 412]. Recently, it has been reported that GSK-3 inhibitors may be used to enhance antigen-specific immunotherapy (antigen-SIT) by the induction of tolerance to an antigen (as "tolerogenic adjuvants"). In fact, it was demonstrated that the combination of CHIR99021 (**32**) and a peptide (*e.g.* myelin basic protein to treat multiple sclerosis) can offer a potential for treatment and/or prevention of diseases associated with pro-inflammatory T cells such as allergies, autoimmune diseases and graft rejection [413]. As well as 6-BIO (**7**), CHIR99021 (**32**) has shown promising results in the generation of cardiovascular cells from human pluripotent cells, through Wnt pathway modulation [414]. The activation of canonical Wnt signaling by GSK-3β inhibition by CHIR99021 (**32**) was exploited to generate cancer stem cells (CSCs) [415], a subpopulation of cancer cells responsible for tumor maintenance, metastasis, therapy resistance, and tumor relapse. A homogenously converted cell population with properties similar to CSCs, including self-renewal capacity and stability, was obtained by combined treatment with CHIR99021 (**32**) and PD184352, a small inhibitor of MAPK able to suppress cell proliferation [416]. The thus-generated CSCs may be used for small molecule drug screening *in vitro* [417]. Since GSK-3 is overexpressed and hyperactivated in NSCLC and plays a role in ensuring the correct alignment of chromosomes on the metaphase plate during mitosis through regulation of microtubule stability, the effects of **32**, alone or in combination with paclitaxel, were studied both *in vitro* and *in vivo*. CHIR99021 (**32**) demonstrated to inhibit the growth of hNSCLC cell lines in a synergistic manner with paclitaxel, supporting its use in taxol-based chemotherapy for human lung cancer treatment [418].

Similarly, Fukunaga and collaborators reported the synthesis of different series of pyrimidinones (**34**, **35**) with a good pharmacokinetic profile and able to inhibit τ phosphorylation in mice after oral administration [419, 420].

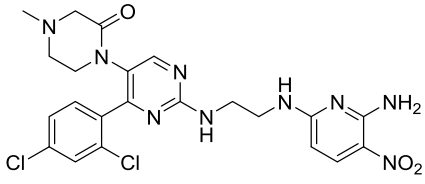
As previously mentioned, staurosporine (**16**) inspired the research of a wide number of maleimide derivatives as GSK-3β inhibitors (Fig. **12**) [421]. Among all, the bisindolylmaleimide Ro 31-8220 (**36**) resulted to be a potent GSK-3β inhibitor, through ATP-competition but also inhibition of voltage-dependent sodium channels [6]. GlaxoSmithKline also focused on the research of GSK-3 inhibitors, identifying different maleimides such as compounds SB415286 (anilinomaleimide) (**37**) and SB216763 (arylindolemaleimide) (**38**). Both compounds (**37**, **38**) stimulate glycogen synthesis in human hepatocytes and induce the expression of β-catenin-LEF/TCF related genes. Moreover, they have shown neuroprotective effects *via* inhibition of PI3K-Akt both *in vitro* and *in vivo* in models of AD, schizophrenia, and HD [384]. Recently, the use of GSK-3 inhibitors **37** and **38** has been proposed to promote immunity in subjects with chronic conditions, such as cancer and infections. In fact, GSK-3β is involved in the control of the transcription of immunosuppressive receptors, such as programmed death 1 (PD-1), and the expression of the transcriptional regulator of Th1, named T-bet, in immune cells [422]. Another study outlined that the inhibition of GSK-3β by compounds **37** and **38** exerts a protective effect on hippocampal neurons from radiation-induced apoptosis, involving regulation of MDM2-dependent p53 accumulation and interactions between GSK-3β, MDM2 and p53 [423]. Furthermore, a radiolabeled derivative of **38**, [^{11}C]SB-216763 (**[^{11}C]38**), has been developed as a positron emission tomography (PET) probe. **[^{11}C]38** has been obtained by radiosynthesis and the authors demonstrated its ability to cross the BBB and enter the CNS in both rodents and nonhuman primates [424], although **[^{11}C]38** was not selective against other structurally similar kinases [46, 425, 426]. Finally, the use of SB216763 (**38**) was extended to ophthalmic clinical applications, based on the evidence that GSK-3β inhibition is required for the activation of DNA ligase IV, thereby facilitating DNA repair and genetic stability in retinal neurons. It was demonstrated that SB216763 (**38**) significantly increased the transcriptional activity of ligase IV in ischemic retinal neurons in



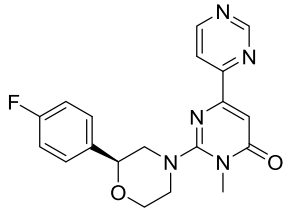
R=Br; X=C Kenpaullone, **27**
GSK-3β = 23 nM
R=NO_2; X=C Alsterpaullone, **28**
GSK-3β = 4 nM
R=Br; X=N Azakenpaullone, **29**
GSK-3β = 18 nM
R=CN; X=N Cazpaullone, **30**
GSK-3β = 8 nM



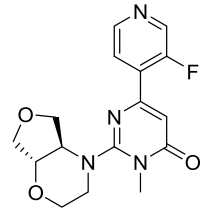
R=H, R_1=NH_2, R_2=NO_2,
CHIR98014, **31**
GSK-3β = 0.58 nM
R=CH_3, R_1=H, R_2=CN, CHIR99021, **32**
GSK-3β = 7 nM



CT20026, **33**
GSK-3β = 4 nM



UDA-680, **34**
GSK-3β = 12 nM



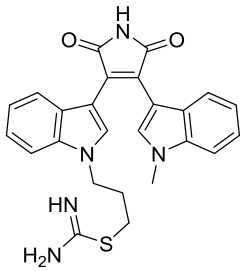
35
GSK-3β = 3.1 nM

Fig. (11). Synthetic ATP-competitive GSK-3 inhibitors (**27**-**35**). Reported data are IC_{50} values.

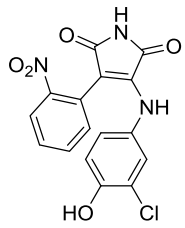
rats, thereby exerting a neuroprotective action [427]. Engler *et al.* reported the discovery of two series of potent and selective maleimides as GSK-3 inhibitors. In particular, compound **39** and **40** inhibit τ phosphorylation in a neuronal cell line and lower plasma glucose in the ZDF rat model of type 2 diabetes [428, 429]. Maleimide 1M (**41**), presenting a polyoxygenated chain, resulted a potent GSK-3β inhibitor (IC_{50} = 17 nM) [430] and robustly enhanced ESC self-renewal [431]. Among this class, compound **42**, with 19-membered macrocyclic structure, was found to be a potent and selective inhibitor of GSK-3β, with a IC_{50} of 3 nM [26].

Recently, a series of aminopyrazoles structurally related to maleimides has been developed. The bisindole-substituted aminopyrazoles were evaluated as GSK-3β inhibitors [432], but unfortunately, this structural modification lead to a large decrease in inhibitory activity, suggesting that the maleimide moiety must be conserved into the inhibitor structure. However, the most promising derivative **43** demonstrated moderate GSK-3β inhibition (IC_{50} = 1.76 μM), and a suppressive effect on glial inflammation and oxidative neurotoxicity. In particular, **43** showed an *in vivo* potent anti-inflammatory effect reducing microglial activation and astrocyte proliferation in the brain of LPS-injected mice [432].

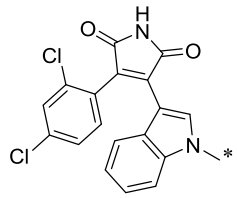
New bisaryl maleimides (**44**, **45**), with high potency and selectivity towards GSK-3β, have been characterized by Ye *et al.* [433, 434]. In particular, compound **45** significantly reduced τ phosphorylation in primary neurons and prevented neuronal death in cerebral ischemic stroke models. *in vivo*, **45** confirmed its neuroprotective activity, reducing infarct size and improving the neurological deficit in cerebral ischemia animal models [434]. A series of benzofuran-3-yl-(indol-3-yl)maleimides was synthesized to improve both GSK-3β inhibitory activity and aqueous solubility. By replacing the indole ring with a diazepinoindole moiety, the highly potent inhibitor **46** has been identified with an IC_{50} value of 13 pM. In the same series, compounds **47** and **48** were identified as potent, nontoxic steroidogenesis stimulators in a steroidogenic cell model, and could find a therapeutic application in the treatment of mood disorders, as GSK-3β inhibition could stimulate neuroactive steroid production, thereby mediating the modulation of anxiety-like behavior *in vivo* [435].



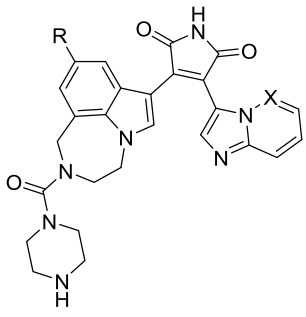
Ro 31-8220, **36**
GSK-3β = 3-38 nM



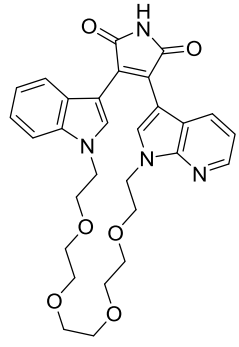
SB415286, **37**
GSK-3β = 78 nM



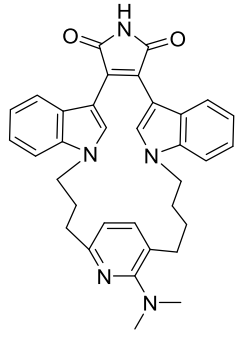
SB216763, **38**
GSK-3β = 34 nM
* = $^{11}CH_3$, **[^{11}C]38**



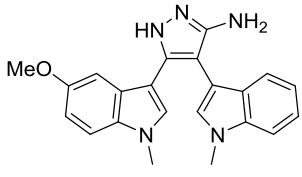
R = H, X = N, **39**
GSK-3β = 0.7 nM
R = F, X = C, **40**
GSK-3β = 1.1 nM



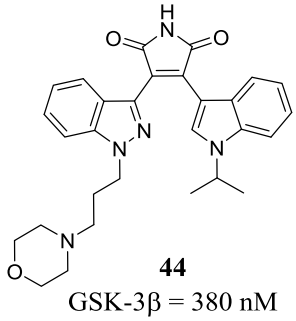
1M, **41**
GSK-3β = 17 nM



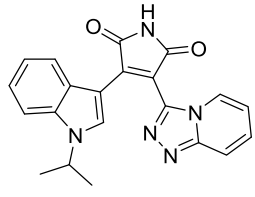
42
GSK-3 = 3 nM



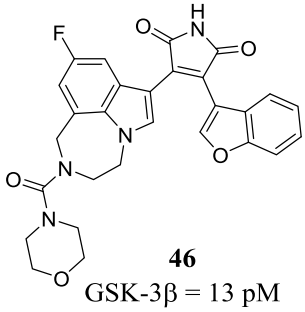
43
GSK-3β = 1.76 μM



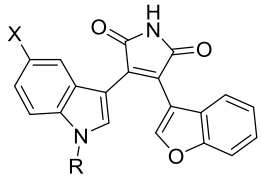
44
GSK-3β = 380 nM



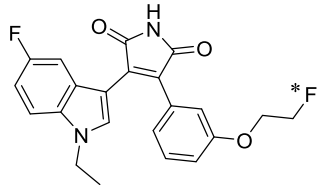
45
GSK-3β = 13 nM



46
GSK-3β = 13 pM



X = Br, R=CH_3, **47**
GSK-3β = 21 nM
X = H, R = -$(CH_2)_2OCH_3$, **48**
GSK-3β = 20 nM



X = F, **49**
GSK-3β = 1.7 nM
* = ^{18}F, **[^{18}F]49**

Fig. (12). Synthetic ATP-competitive maileimedes and bis-indoles as GSK-3 inhibitors (**36**-**49**). Reported data are IC_{50} values.

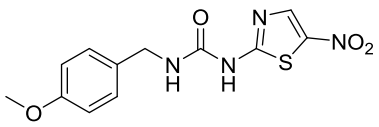
A series of maleimide-based GSK-3β inhibitors containing a fluoroethyl group and candidates for *in vivo* PET imaging of the CNS was recently synthesized. The highly potent GSK-3β inhibitor **49** with nanomolar IC_{50} value was identified and its [^{18}F]-labeled analog, **[^{18}F]49**, obtained by radiosynthesis. *in vivo* PET-computed tomography (PET-CT) imaging studies in rodents showed that **[^{18}F]49** enters the rodent brain [436].

The thiazole AR-A014418 (**50**) is another ATP-competitive inhibitor developed by AstraZeneca (Fig. **13**) [22]. It inhibits GSK-3 with an IC_{50} value of 104 nM and is selective for CDK2, CDK5, and many other kinases. AR-A014418 (**50**) showed to inhibit PI3K and other apoptotic pathways, thus exerting a neuroprotective action. It has shown beneficial effects in models of AD (prevention of A*β*-dependent neurodegeneration) and SLA (decreased motor neurons death and improved cognition). AR-A014418 (**50**) has also shown anti-depressive and antimanic activities in mice. A structurally closed related compound (**51**) showed increased selectivity towards a wide panel of kinases and reduced toxicity in a zebrafish embryo phenotype assay compared to AR-A014418 (**50**) [437]. In order to enhance kinase-selectivity by exploiting the covalent interaction of inhibitors with Cys199, a unique residue in the GSK-3β ATP binding pocket, an electrophilic warhead was incorporated onto the ring scaffold of 1-aryl-3-(4-methoxybenzyl)ureas and a nanomolar GSK-3β inhibitory activity was measured for inhibitor **52**. Even if their results support the hypothesis of a covalent interaction, the authors do not fully confirm it, and more extensive studies are needed to better characterize the nature of the inhibition [438]. Takeda pharmaceuticals reported the synthesis and characterization of 1,3,4-oxadiazole derivatives as GSK-3β inhibitors (**53**, **54**). **53** showed high selectivity and potency for GSK-3β inhibition with an IC_{50} value of 2.3 nM. Co-crystallization of **53** and GSK-3β showed hydrogen-bonding interactions between the benzimidazole moiety and the hinge region of GSK-3β, and additional interaction between the oxadiazole and the Arg 141 residue on GSK-3β. MMBO (**54**) presents good water solubility, oral bioavailability, and BBB permeability; it has been assayed in neuronal cell cultures and triple transgenic mice (3xTg-AD, mice overexpressing hyperphosphorylated τ, mutant form of PS-1 and APP) and has proven to be effective in reducing τ phosphorylation both *in vitro* and *in vivo* [29, 439]. The 1,3,4-oxadiazole–1,2,3-triazole **55** is a nanomolar inhibitor of GSK-3β that showed maximum antidepressant activity in forced swim test (FST) and tail suspension test (TST) models, resulting more effective than fluoxetine [440]. GS87 (**56**) is a novel 1,3,4-oxadiazole GSK-3 inhibitor, with IC_{50} values in the nanomolar range for both α and β isoforms, identified to discover a small molecule optimized against AML. GS87 (**56**) demonstrates high efficacy to induce differentiation with selective growth inhibition of leukemic cells in a mouse AML model system, probably due to the activation of GSK-3-dependent signaling components including MAPK signaling [441].

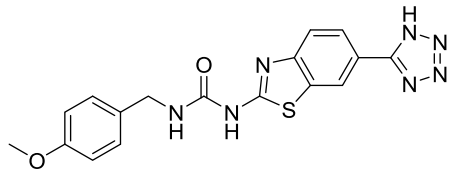
A library of aryl and heteroaryl substituted *N*-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,4-oxadiazole-5-carboxamide derivatives was designed and synthesized by Koryakova *et al.* [442] and within this class of molecules ATP-competitive compound **57** turned out to be the more potent and selective inhibitor of GSK-3β with an IC_{50} of 0.35 μM.

Mitsubishi Pharma reported a series of benzofurazan-derived potent GSK-3 inhibitors presenting the less common furazan (*e.g.* 1,2,5-oxadiazole), the most potent of which is compound **58** (Fig. **13**) [443, 444]. The same research group, in collaboration with Sanofi-Aventis, identified a novel potent GSK-3β nanomolar inhibitor bearing a pyrimidinone scaffold, SAR502250 (UDA-680) (**59**) [419, 445]. In P301L human τ transgenic mice, SAR502250 (**59**) attenuated τ hyperphosphorylation in the cortex and spinal cord, and behavioral studies indicated its administration in aged mice after infusion of A*β*25–35 improved the cognitive deficit [446]. Potent inhibition of GSK-3β was achieved by transforming the morpholine moiety into a piperazine ring, whose nitrogen atom establishes a hydrogen bond with the oxygen atom of the main chain of Gln185 [447]. However, no compounds showed desirable *in vitro* pharmacokinetic profiles. Further structure optimization studies led to compound **60,** a very potent inhibitor with subnanomolar IC_{50}, with a phenyl group on the piperazine nitrogen atom and a methyl group on the piperazine ring able to make cation-π and CH-π interactions, respectively, with GSK-3β [448].

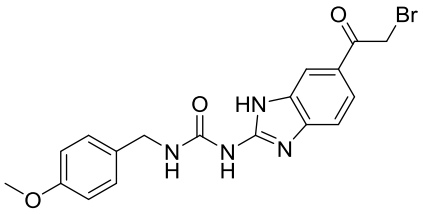
Very recently, Martinez and coworkers presented an *in silico* design, screening and *in vitro* validation of potent GSK-3β type II inhibitors, specifically designed to target the DFG-out inactive conformation of the enzyme [449]. Type II inhibitors have the potential for greater selectivity than classical ATP-competitive (Type I), due to the structural heterogeneity of the hydrophobic allosteric site immediately adjacent to the ATP-binding site, accessible in the DFG-out conformation. First, the computational models led to identify the (pyrimidin-2-yl)amino-furo[3,2-*b*]furyl-urea scaffold. The following assays allowed to select the most potent and selective GSK-3β inhibitors of this series, in



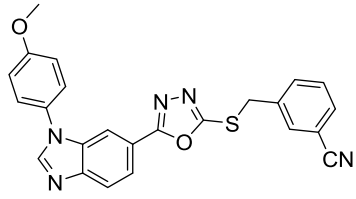
AR-A014418, **50**
GSK-3β = 104 nM



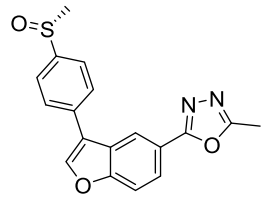
51
GSK-3β = 140 nM



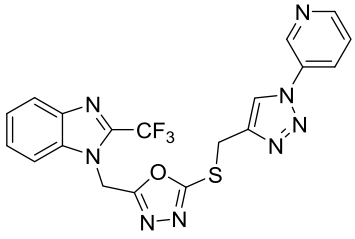
52
GSK-3β = 130 nM



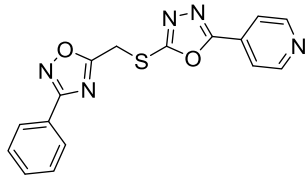
53
GSK-3β = 2.3 nM



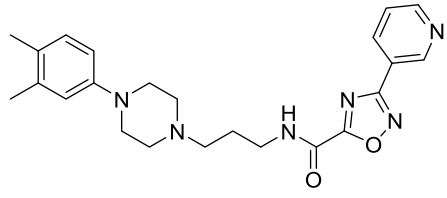
MMBO, **54**
GSK-3β = 53 nM



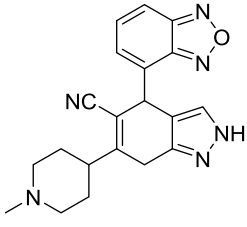
55
GSK-3β = 150 nM



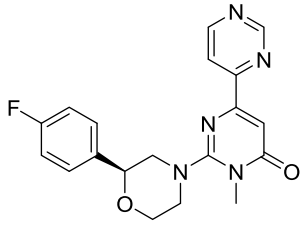
GS87, **56**
GSK-3α = 415 nM
GSK-3β = 521 nM



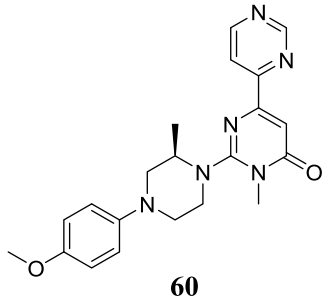
57
GSK-3β = 350 nM



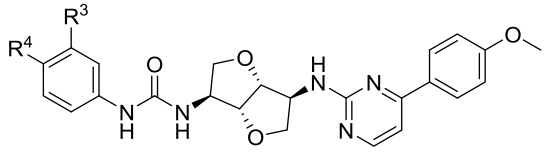
58
GSK-3β = 2.5 nM



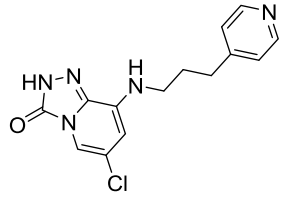
SAR502050 (UDA-680), **59**
GSK-3β = 12 nM



60
GSK-3β = 0.1 nM



R^3 = CN, R^4 = H, **61**
GSK-3β = 87 nM
R^3 = H, R^4 = $COCH_3$, **62**
GSK-3β = 412 nM



63
GSK-3β = 111 nM

Fig. (13). Synthetic ATP-competitive GSK-3 inhibitors (**50**-**63**). Reported data are IC_{50} values.

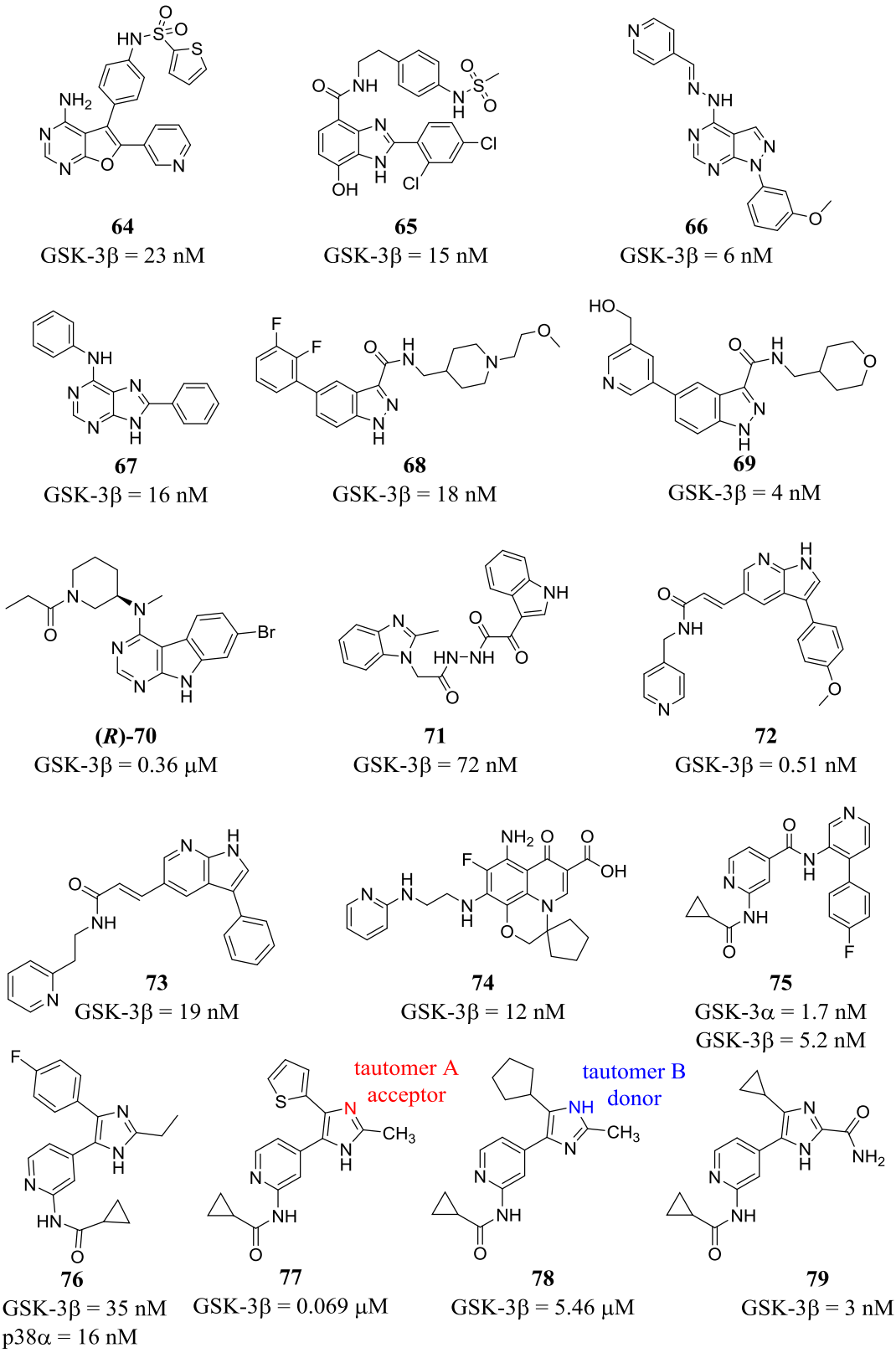


Fig. (14). Synthetic ATP-competitive GSK-3 inhibitors (**64-79**). Reported data are IC_{50} values. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

particular compounds **61** and **62**, with good selectivity for GSK-3β inhibition and promising neuroprotective effects in an okadaic acid (OA)-induced neurodegeneration cell model at low micromolar concentrations.

The crystal structure of staurosporine (**16**) in the ATP binding pocket of GSK-3β has allowed the study of the interactions between the inhibitor and the enzyme and the design of several molecules that mimic this binding mode. Among them, the 8-amino- [1, 2, 4]triazolo[4,3-*a*]pyridin-3(2*H*)-one derivative **63** showed good potency towards GSK- 3β (IC_{50} = 111 nM), good water solubility (>10 mg/mL), good permeability of the BBB and oral pharmacokinetic profile [450].

In these years, many heteroaromatic bicyclic cores emerged as suitable scaffolds for the synthesis of ATP--competitive GSK-3β inhibitors. Some examples are furo[2,3-*d*]pyrimidines (**64**) [451], benzimidazoles (**65**) [25], pyrazolo-pyrimidines (**66**) [452] and purines (**67**) [453] (Fig. **14**).

A bicyclic moiety is also the core of the indazole derivative **68** identified following a virtual screening program [83], which showed efficacy *in vivo* in the low-dose amphetamine test, a model used to mimic mania, a key symptom of mood disorders [454]. Compound **68** showed a favorable preclinical profile, but further progression was prevented by its activity at the hERG ion channel (IC_{50} = 44 nM). To retain the good *in vivo* and *in vitro* profile of **68** while reducing the binding at the hERG ion channel, the structure was optimized by reducing both its lipophilicity and basicity which are responsible for the lack of selectivity of **68**. This approach led to compound **69** that demonstrated an excellent enzymatic and cellular GSK-3β inhibitory potency and reduced hERG activity (IC_{50} > 100 μM), and in addition, promising *in vitro* ADME properties along with a favorable kinase selectivity profile [53]. With the aim of improving both the BBB permeation and enhancing CNS penetration, the same research group at Angelini Pharma investigated a scaffold alternative to indazole, by a structure-based approach and fine-tuning of physicochemical properties, identifying imidazo[1,5-*a*]pyridine-1-carboxamide and imidazo[1,5-*a*]pyridine-3-carboxamide [55]. Despite the improvement of ADME properties of imidazo[1,5-*a*]pyridines, all new compounds resulted in less potent GSK-3β inhibitors than the corresponding indazole derivatives. The low acidity of the hydrogen in the imidazole ring and the unfavorable geometric rearrangement affect H-bond donating abilities and reduce the affinity for GSK-3β, instead the indazole acidic hydrogen has a key role for a tight interaction within the ATP pocket of the enzyme [55].

Enantiopure compound **(*R*)-70** is the most potent of a series of pyrimido-indole derivatives, with a potency towards GSK-3β in the submicromolar concentration range (IC_{50} = 0.36 μM). Interestingly, the stereo configuration strongly influenced the inhibitory activity, being (*R*)-enantiomers more potent inhibitors of GSK-3β with respect of (*S*)-counterparts [455]. The neuroprotective effects of **(*R*)-70** were investigated in SH-SY5Y cells against the neurotoxicity induced by neurotoxins, such as hydrogen peroxide, to mimic general oxidative stress, and Aβ42 oligomers as an AD model. ***(R)*-70** significantly decreased the neurotoxicity elicited by hydrogen peroxide but was ineffective on Aβ42 oligomers-induced neurotoxicity.

A very peculiar carbohydrazide moiety is present in derivative **71**, a nanomolar GSK-3β inhibitor that demonstrated *in vivo* antidepressant activity evaluated in the tail suspension test (TST) and forced swim test (FST) [456].

Notably, the 1*H*-pyrrolo[2,3-*b*]pyridine derivative **72**, developed with a fragment-based *de novo* design procedure, showed an IC_{50} value in the subnanomolar range and high selectivity [457]. Starting from an initial hit compound with IC_{50} of 1.45 μM and applying a fragment-linking strategy, the research group identified the potent GSK-3β inhibitor **73** (IC_{50} = 19 nM) [458].

A different chemotype is represented by spiroquinolone **74** (IC_{50} = 12 nM) that showed a reducing effect on plasma glucose concentration in a dose-dependent manner in mice [459].

Recently, a novel class of isonicotinamide GSK-3 inhibitors has been patented. Compound **75** is active towards both α and β isoforms but resulted very selective towards a wide panel of kinases. In fact, the substituent at the 4 position of the 3-aminopyridine nucleus binds to the sugar pocket of the ATP binding site that is not highly conserved among different kinases. Moreover, it has shown good *in vivo* activity lowering p-*τ* levels in a triple transgenic AD mouse model after oral administration [43].

Heider F. *et al.* developed a series of pyridinylimidazoles as dual GSK-3β/p38α mitogen-activated protein kinase inhibitors [460]. The connection between p38α MAP kinase and AD was demonstrated by the increased levels of phosphorylated p38 in postmortem human brain tissue from AD patients [461]. Furthermore, it has been hypothesized that the kinase is also involved in the hyperphosphorylation of τ proteins [462]. Consequently, a dual GSK-3β/p38α mitogen-activated protein kinase inhibitor could be considered a useful

tool for the treatment of AD. Therefore, several imidazole derivatives have been reported [460], and among them, compound **76** resulted to be the most potent dual-target-directed inhibitor, showing IC_{50} values in the nanomolar concentration range. (p38α, IC_{50}=16 nM; GSK-3β, IC_{50}= 35 nM). **76** possessed also an excellent metabolic stability and a quite good selectivity over the closely related GSK-3α isoform.

Starting from these results, a series of 2-methyl-imidazoles has been developed with the aim of obtaining GSK-3β selective inhibitors. Interestingly, 2-methylimidazole's tautomeric state is fundamental for compound activity. In fact, the results of quantum mechanics calculations assessing the probability of different tautomeric states and conformations suggest that the more active compounds generally prefer tautomer A and are nanomolar inhibitors, while the less active ones present a significantly less fraction of tautomer A (Fig. **14**, compounds **77** and **78**). To overcome the tautomeric effect, carboxamide has been introduced instead of methyl to gain interactions with the amide oxygen of Lys85. Among them, **79** was the most active, displaying GSK-3β inhibition in the nanomolar concentration range, with very good kinase selectivity as well as metabolic stability and GSK-3β inhibition effect in neuronal SH-SY5Y cells [463]. Anyhow, molecular dynamics simulations showed that **79**, regardless of imidazole's tautomeric state, stabilizes the binding with GSK-3β *via* carboxamide-mediated water-network interactions near Asp200. The pyridin-2-yl cyclopropanecarboxamide moiety is also present in compound **80** (Fig. **15**), a GSK-3β inhibitor with IC_{50} in the subnanomolar range, which showed significant p-τ reduction when dosed orally in a triple transgenic AD mouse model [42].

The potent and selective ATP-competitive GSK-3 inhibitor **81** belongs to a series of 5-nitro-N2-(2-(pyridine-2-yl-amino)ethyl)pyridine-2,6-diamines. In a panel of 442 kinases, it turned out that **81**, tested at a concentration of 10 μM, inhibited more than 90% GSK-3α and GSK-3β activities, and that of the other four kinases (JNK1, JNK2, JNK3, and B-RAF) tested [54]. X-ray crystallography of the co-structure of **81** bound to human GSK-3β (PDB ID 6V6L) revealed that the compound occupies the volume of the kinase active site, the kinase maintains an active DFG-in conformation, and the ethylene diamine linker is crucial to orient the 2,4-dichlorophenyl group to form fundamental hydrophobic interactions by positioning the chloro groups both in a hydrophobic 'dimple' within the P-loop, and in a hydrophobic pocket at the bottom of the ATP binding pocket [54].

Among the unconventional scaffolds, the pyrazolo-tetrahydroquinolinone scaffold, as present in compound BRD1652 (**82**), led to highly selective and potent GSK-3α/β inhibitors. BRD1652 (**82**) caused attenuation of τ and collapsin response mediator protein-2 (CRMP-2) phosphorylation and stabilization and nuclear translocation of β-catenin. Moreover, it demonstrated efficacy *in vivo* against amphetamine-induced hyperactivity (AIH), a model of dopaminergic-induced motor activation [45]. The same authors, taking advantage of the Asp-Glu "switch" in GSK-3 (Asp^{133}→Glu^{196} in the kinase hinge of GSK3β and GSK3α, respectively) and by mean of a structure-based design, optimized the substituent on the pyrazole ring to maximize the differences within the pockets of GSK-3α and GSK-3β to obtain paralog-selective inhibitors. The structure optimization led to BRD3731 (**83**) and BRD0705 (**84**), with opposite selectivity, since the neopentyl derivative **83** displayed 14-fold selectivity for GSK-3β (GSK-3β, IC_{50} = 15 nM; GSK-3α, IC_{50} = 215 nM), while **84,** with no substituent in the same position, maintained inhibitory potency and displayed an eight-fold selectivity for GSK-3α versus GSK-3β (GSK-3α, IC_{50} = 66 nM; GSK-3β, IC_{50} = 515 nM) [47]. The authors showed that, in AML cell lines, potent inhibition of GSK-3α versus GSK-3β was achieved with a ~10--fold selectivity, with no effect on β-catenin stabilization. Considering that β-catenin overexpression is associated with several types of cancer, compounds exerting selective GSK-3α inhibition could be potentially effective therapeutic anticancer agents [47].

Finally, it is worth mentioning some inhibitors that are not structurally related to all of the classes discussed above. Recently, a series of triazolo-thiadiazine was identified as GSK-3β inhibitors, and the most potent compound (**85**) showed inhibition in a micromolar concentration range [464]. Instead, inhibitor **86** was identified through a virtual high-throughput screening (vHTS) of a commercially available small molecule collection of 50,000 compounds, and it is a benzoxazinic micromolar GSK-3β inhibitor [465]. Compound **87** is a novel oxazolo[5,4-*f*]quinoxalines-based potent GSK-3β inhibitor with an IC_{50} in the nanomolar range [466]. Finally, a series of compounds designed starting from the natural β-carboline alkaloid harmine was recently described. The most interesting one, the compound ZDWX-25 (**88**), is a potent inhibitor of GSK-3β and DYRK1A, with IC_{50}s in the nanomolar range, capable of good blood-brain barrier permeability *in vitro*, inhibition of hyperphosphorylation of τ protein in okadaic acid (OKA)-induced SH-SY5Y cells, and improvement of impaired learning and memory in APP/PS1/τ

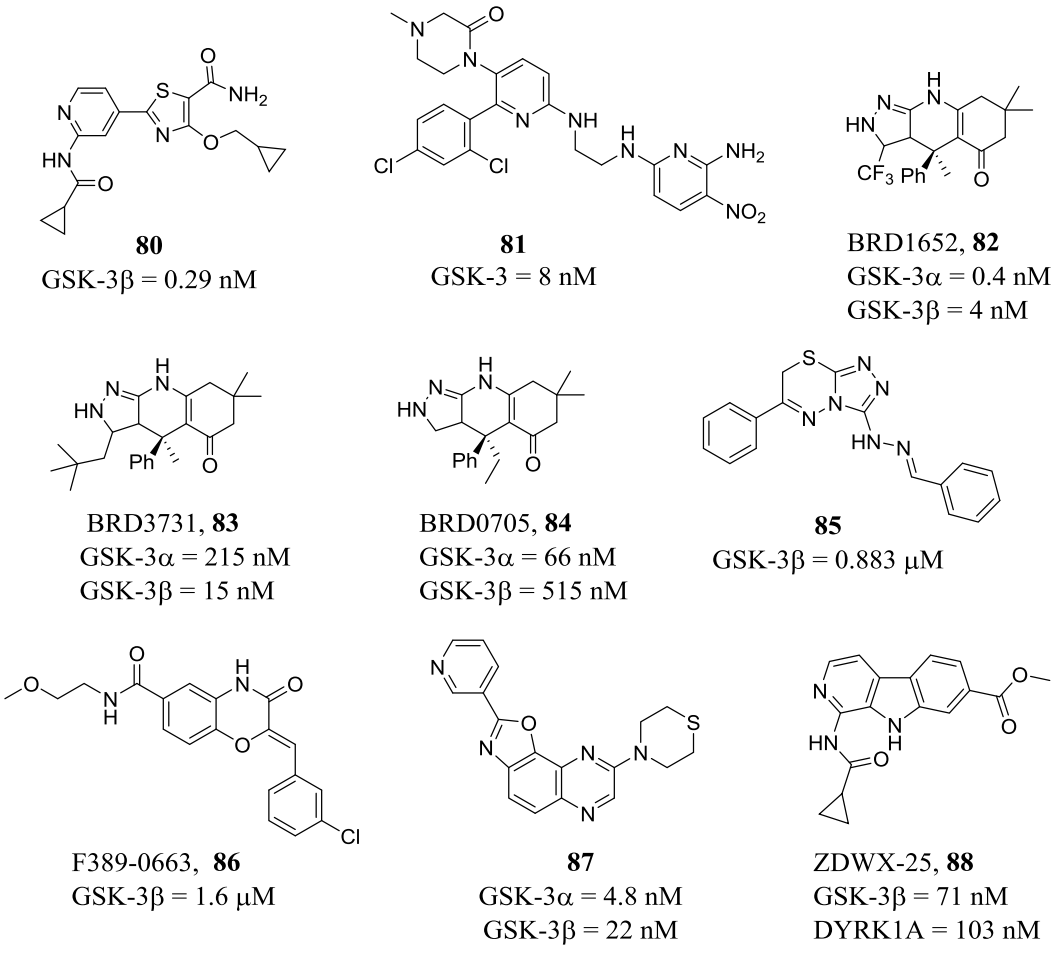


Fig. (15). Synthetic ATP-competitive GSK-3 inhibitors (**80**-**88**). Reported data are IC_{50} values.

transgenic mice. Since DYRK1A is the initiating kinase of the GSK-3β-mediated τ phosphorylation, simultaneous inhibition of both kinases could prevent τ hyperphosphorylation, restore the normal function of τ protein and inhibit NFTs generation [467].

5.4. Non-ATP Competitive Inhibitors

Most of the GSK-3β inhibitors discovered so far bind to the enzyme in the ATP cleft, with a reversible and ATP competitive mechanism of action. Since the ATP-binding site is highly conserved, these inhibitors often lack selectivity for the similarity of ATP binding sites between kinases [468, 469]. In addition, the affinity for this pocket is usually very high, thus ATP-competitive inhibitors are generally able to inhibit the enzyme in a very potent form at lower concentrations. GSK-3β is a ubiquitous enzyme whose activity is necessary for many different processes, consequently, a strong inhibition could cause undesired side effects. In recent years, many efforts have been done to identify non-ATP competitive GSK-3 inhibitors, which bind to the protein in a more subtle way. In fact, substrate competitive inhibitors act by blocking GSK-3 activity through the binding to the GSK-3 substrate-binding site [470], while allosteric inhibition is accomplished through binding to an allosteric binding site of the enzyme, presumably distinct from both the ATP- and substrate-binding site, that cause conformational changes in the enzyme and reduce its activity [471]. Even irreversible or covalent reversible inhibition is a non-ATP competitive mechanism of action. Due to the presence of Cys199 in the ATP binding pocket, several compounds were developed to target this less conserved residue among kinases with the scope to enhance potency and selectivity towards GSK-3β [472].

5.4.1. Natural Origin Non-ATP Competitive Inhibitors

Among the non-ATP competitive GSK-3β inhibitors, the natural alkaloid Manzamine A (**89**) [473] and the linear furanosesquiterpene Palinurin (**90**) [474], both extracted from marine sponges, have been described (Fig. **16**). The non-ATP competitive inhibitory mechanism of Manzamine A has been demonstrated experimentally, and a computational study proposed that **89** could bind to the substrate recognition region [471]. Manzamine A (**89**) inhibits GSK-3β and CDK5 with IC_{50} values of 10 and 1.5 μM, respectively. It was reported that **89** decreased τ hyperphosphorylation in human neuroblastoma cell lines (SH-SY5Y cells), thus interfering with τ pathology [475] and was evaluated also for antimalarial and antimicrobial activity [476]. On the other hand, the mechanism of inhibition suggested for Palinurin (**90**) seems to be allosteric: in fact, it seems that the molecule binds the N-terminal portion of the enzyme, influencing the orientation of the third and fourth strand of the β sheet and the hydrogen bond usually formed between Ser66 and the γ phosphate of ATP, thus preventing the correct positioning of the substrate to this portion of the enzyme [474].

5.4.2. Synthetic Non-ATP Competitive

In the early 2000s, Martinez *et al.* reported the first class of non-ATP competitive GSK-3β inhibitors, thiadiazolidindiones. TDZD-8 (**91**), considered one of the most interesting pharmacological tools together with the closely related Tideglusib (**3**), are reversible covalent inhibitors of GSK-3β that target Cys199 located at the entrance of the active site [314]. Once the disulfide bond between the enzyme and the TDZD derivative is formed, the thiadiazolidinone core decomposes into carbon monoxide and the corresponding *N,N′*-disubstituted urea, which could present a residual activity towards the kinase. In fact, the *N*-naphtyl-*N′*-benzylurea (**92**), which derives from Tideglusib (**3**), resulted to inhibit GSK-3β with an IC_{50} value of 17.1 μM, thus contributing to the long-lasting activity of this compound [315, 477]. Recent studies based on computational analysis suggested that TDZD-8 (**91**) would not show an affinity for the active form of GSK-3β, which appears to lack any allosteric hydrophobic pocket, but instead it might bind to a hydrophobic pocket in the inactive DFG-*out* form of the kinase, similarly to Imatinib that targets Abl kinase in its inactive form [478]. TDZD-8 (**92**) demonstrated neuroprotective activity *in vitro*, as it can reduce the phosphorylation of τ protein, and antidepressant activity in different animal models. In zebrafish with a okadaic acid-induced AD model, TDZD-8 (**91**) treatment was able to restore cognitive disfunction, reduce the expression of p-τ, decrease mortality, restore the activity of PP2A [479]. In a rat model of spinal cord injury, administration of **91** was found to significantly inhibit neuronal apoptosis and promote neuronal cell regeneration [480, 481]. Other authors reported TDZD-8 (**91**) acts as a protective agent in multiple murine models of disease such as arthritis [482], and colitis [483], it induces death of several major forms of leukemia cells including malignant myeloid stem and progenitor populations [483], has potent anti-proliferative and proapoptotic effects on glioma cells *in vitro* and *in vivo* [484], and significantly inhibits tumor growth in mouse xenograft models of prostate cancer [485].

COB-187 (**93**) is a reversible inhibitor of GSK-3 recently identified by Noori *et al.* COB-187 (**93**) inhibited GSK-3α and GSK-3β with nanomolar potency (IC_{50} of 22 nM and 11 nM, respectively) and demonstrated high selectivity in a molecular screen of a panel of 404 kinases, where it showed inhibition of only 3 kinases, while in the same assay Tideglusib (**3**) inhibited 50 kinases to the same extent [486]. COB-187 (**93**) was found to reversible inhibit GSK-3β *via* an induced-fit mechanism, with a low k_{off}, and a time and Cys-199-dependent mechanism, suggesting a non-ATP competitive mechanism [487].

Another family of non-ATP competitive inhibitors is the halomethylketones (HMKs) group, including HMK-32/DIP3.18 (**94**). HMKs inhibit the enzyme in an irreversible manner by the formation of a carbon-sulfur covalent bond between the methyl ketone moiety and the thiol of Cys199 [488]. The covalent and irreversible binding to the kinase was also confirmed through model reactions, docking studies, and mass spectrometric analysis of the resultant product. Moreover, Perez *et al.* reported that the introduction of the halomethylketone warhead is able to convert a reversible inhibitor (**95**, **96**) into a more potent irreversible GSK-3 inhibitor (**97**, **98**) [489]. Recently, the potent indolyl maleimide covalent inhibitor **99** with a mild α-fluoromethyl amide reactive group has been reported [490]. Preliminary results showed a good selectivity of **99** for GSK-3β over a panel of 44 kinases. Compound **99** could act as a covalent probe in cellular and animal models for studying of the roles of GSK-3β in several diseases.

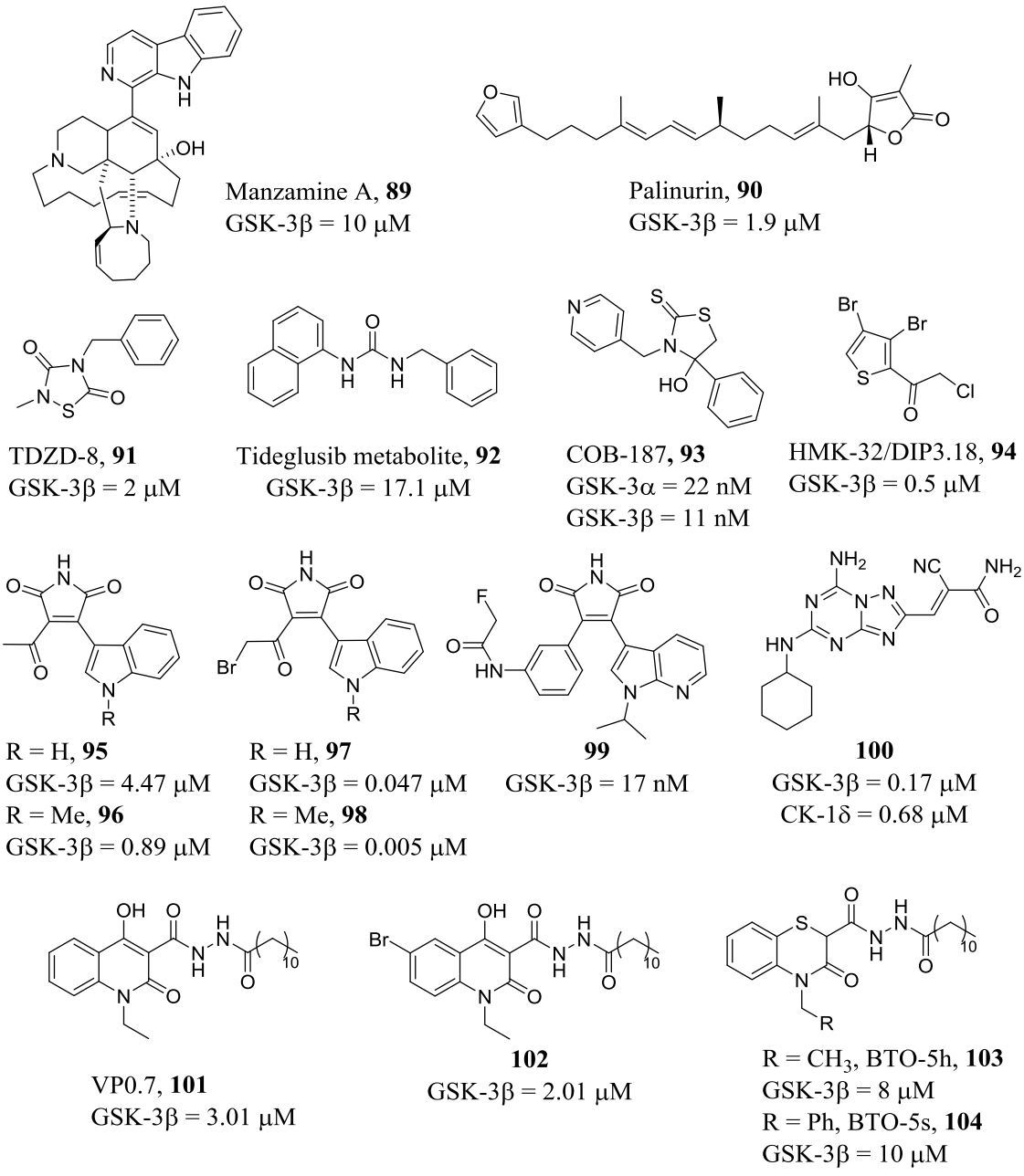


Fig. (16). Non-ATP competitive GSK-3 inhibitors (**89**-**104**). Reported data are IC_{50} values.

Redenti *et al.* described a triazolo-triazine derivative (**100**) that showed a combined inhibitory activity against GSK-3β and CK-1δ, with IC_{50}s of 0.17 μM and 0.68 μM, respectively [51]. Compound **100** behaves with two different mechanisms of action: a classical ATP competition against CK-1δ and a covalent inhibition with GSK-3β, confirmed by the X-ray structure of co-crystal of compound **100** inside GSK-3β that revealed the covalent interaction between the cyanoacrylamide warhead of **100** and Cys199 of the kinase. Preliminary studies on *in vitro* models of Parkinson's disease revealed that compound **100** is not cytotoxic and shows neuroprotective activity [51]. Further studies are needed to establish if the inhibition of GSK-3β and CK-1δ is a valuable strategy for neurodegenerative diseases and neuroinflammatory disorders treatment.

Different allosteric binding sites have been described on the GSK-3 surface, which could be targeted for selective inhibition of the enzyme. In particular, the quinoline-3-carbohydrazide derivative VP0.7 (**101**, IC_{50}= 3.01 μM) is considered the first allosteric inhibitor of GSK-3. **101** showed neuroprotective activities *in vitro*, while its activity *in vivo* has been presented in preclinical models of fragile X syndrome and multiple sclerosis [315, 471]. More recently, the same authors, starting from VP0.7 (**101**) scaffold, reported the synthesis, SAR, and binding mode studies of a family of quinoline-3-carbohydrazide derivatives [491]. These compounds bind to an allosteric binding site of GSK-3β, modifying the flexibility of the activation loop and thus inducing a smooth conformational change in the active site, and a consequent decrease in kinase activity. The subtle modulation of the enzyme may be advantageous in preventing side effects derived from β-catenin signaling interference which are associated with strong GSK-3β inhibition [492]. In this series, compound **102** showed inhibition in the low micromolar concentration range (IC_{50} = 2.01 μM) and has been tested in rare neuromuscular diseases, such as congenital myotonic dystrophy type 1 (CDM1) and spinal muscular atrophy (SMA), where it showed an improvement of delayed myogenesis in CDM1 along with a neuroprotective effect in SMA-derived cells [491].

VP0.7 (**101**) has been used as a starting point also by Zhang *et al.* that reported two benzothiazinone (BTO) derivatives as GSK-3β inhibitors (**103**, **104**), presenting two different inhibitory mechanisms. BTO-5h (**103**) is, in fact, an allosteric modulator of GSK-3β, while BTO-5s (**104**) is a novel substrate competitive inhibitor. Compounds **103** and **104** showed good efficacy and selectivity towards a panel of related protein kinases. Moreover, both compounds have been able to reduce glycogen synthase phosphorylation levels in an intact cell and greatly enhance the glucose uptake in both HpG2 and 3T3-L1 cells [493].

5.4.2.1. Substrate Competitive Inhibitors

Since GSK-3β requires preferentially pre-phosphorylated substrates, many efforts have been directed to the synthesis of peptides showing a similar sequence to the one usually recognized by the kinase. The first example is L803-mts (**105**) (Fig. **17**), which is a cell-permeable phosphorylated peptide composed of 11 residues derived from the GSK-3 substrate heat shock factor-1 (HSF-1) with a myristic acid attached to the N-terminal end that enables cell permeability [315]. Computational studies helped to clarify the interactions between the peptide and the kinase and revealed that **105** does not occupy exactly the same site occupied by the substrate. Both interact with the phosphate binding region, but while the substrate binds mainly to the cavity delimitated by Gln89 and Asn95, L803-mts (**105**) interacts with Phe93 and a hydrophobic portion of the enzyme, away from the ATP-binding site [315]. Administration of L803-mts (**105**) in *in vivo* models of diabetes led to an improvement in glucose tolerance and a decrease of insulin levels; **105** also demonstrated neuroprotective properties both *in vitro* and *in vivo* [315]. Licht-Murava *et al.* reported a new type of GSK-3 inhibitor, L807-mts (**106**), that acts through a substrate-to-inhibitor conversion mechanism that occurs within the catalytic site of the enzyme. In specific, peptide **106** binds GSK-3 (α or β) as a substrate and after phosphorylation is converted into an inhibitor [494]. Compared to L803-mts (**105**), L807-mts (**106**) is more potent, highly selective *in vitro*, and it exhibits suitable pharmacological properties in mice, including stability, brain permeability, pharmacokinetics, and safety. Moreover, L807-mts (**106**) enhanced the clearance of Aβ masses, reduced inflammation, and improved cognitive and social skills in the 5XFAD AD mouse model [494]. Two peptide GSK-3 inhibitors, derived from Frat (FRATide-39 residues) [15] or Axin ($GID_{320-429}$, $GID_{380-404}$), are described but their therapeutic relevance is much less important than small peptides [495]. Recently, the 44-mer peptide hDISCtide, derived from the human DISC1 protein, was identified. hDISCtide is a selective GSK-3β inhibitor (IC_{50} of 95 nM), with a noncompetitive inhibition mechanism to both ATP and substrate peptide [496].

5-imino-1,2,4-thiadiazoles (ITDZs) were the first non-peptidic compounds able to inhibit GSK-3 in a substrate competitive manner [497]. ITDZs were obtained modifying the skeleton of the TDZD compounds (**91**): two carbonyl groups at the 3 and 5 positions of the thiadiazole ring were in fact replaced with imino and alkyl/aryl moieties. Docking studies have shown that ITDZs (here represented by compound **107**) interact with GSK-3 protein through a hydrogen bond between the proton of the imino-charged group and the backbone oxygen of Phe67 and an aromatic S-π interaction between the thiadiazole scaffold and the aromatic ring of the Phe67. The ITDZs resulted able to cross the BBB, they show a high affinity for albumin and, in general, a good pharmacokinetic profile. ITDZs, including **107**, have been shown to exert neuroprotective actions against different cell cultures of astrocytes and microglia treated with LPS. Moreover, ITDZs presented efficacy in promoting murine neural stem cells' differentiation and repairing damaged neuronal areas [498].

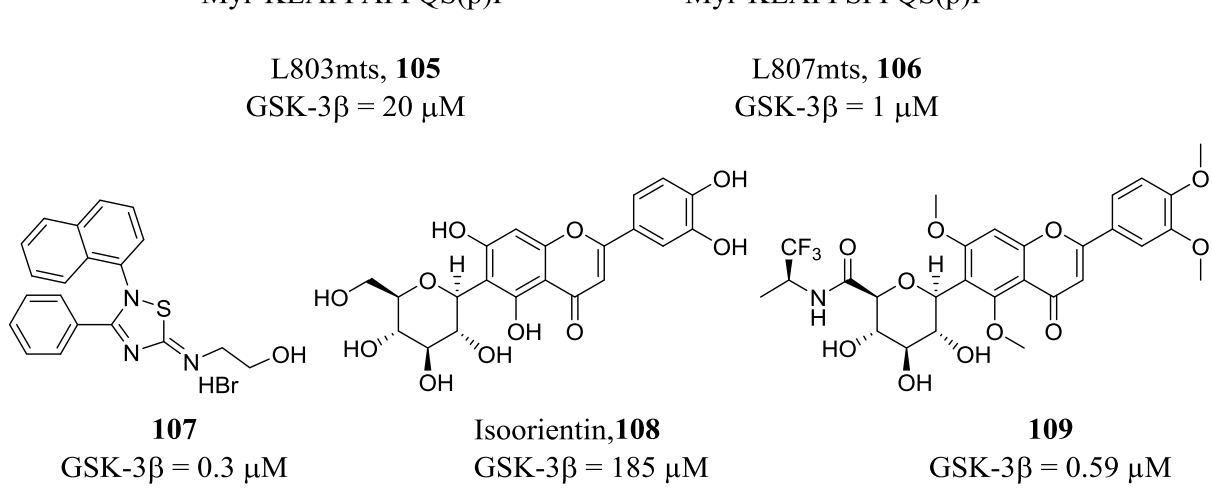


Fig. (17). Substrate competitive GSK-3 inhibitors (**105**-**109**). Reported data are IC_{50} values.

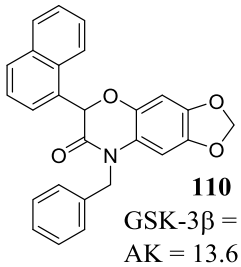
6-C-Glycosylflavone isoorientin (**108**), containing the aglicon luteolin (**11**) as the flavone core, is a natural compound isolated from corn silk (*Zea mays*), that exerts specific inhibition of GSK-3β in a substrate competitive mode, although with low potency (IC_{50} = 185 μM) [46]. *in vitro* cellular studies pointed out that **108** attenuated τ phosphorylation mediated by GSK-3β and exerted neuroprotective effects against β-amyloid induced τ hyperphosphorylation and neurotoxicity in SH-SY5Y cells [46]. Currently, the neuroprotective properties of **108** are under investigation for potential applications in AD and PD therapy [499, 500]. Starting from the isoorientin **108**'s scaffold, a series of semisynthetic 6-C-Glycosylflavones have been semisynthesized to target the substrate site on GSK-3β [501]. In particular, **109** was obtained from **108** by introducing a hydrophobic amide group on the primary alcohol of the C-glycon, which is supposed to address a concave cleft critical for substrate recognition [502], and by methylating the phenolic hydroxyls to improve bioavailability, metabolic stability, and potency. **109** (IC_{50} = 0.59 μM) shows a potency improvement by 310-fold *versus***108** and it effectively attenuates τ hyperphosphorylation and amyloid neurotoxicity in molecular and cellular AD models.

5.5. Multitarget Inhibitors

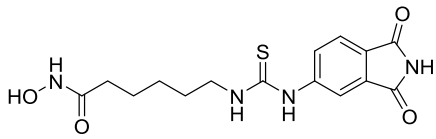
The concept of multitarget drug for the treatment of several pathologies is a well-known approach used in therapy, in particular for the treatment of infections or cardiovascular disorders. However, the concept of polypharmacology applied to neurodegenerative disorders could be considered an innovative approach that has been strongly investigated in the last decades [503-508]. As already mentioned, GSK-3β seems to play an important role in neurological disorders such AD [509-511]. Therefore, it is obvious to hypothesize that a synergic effect of GSK-3β inhibition with other targets potentially involved in neurodegeneration could represent a new interesting tool for the treatment of neurological disorders. In particular, in this section we want to briefly summarize the recent research developments on multitarget ligands with GSK-3β inhibitory activity and the interactions with other biological targets involved in neurodegenerative disorders (Fig. **18**) [504, 512, 513].

5.5.1. Dual GSK-3β/AK Inhibitors

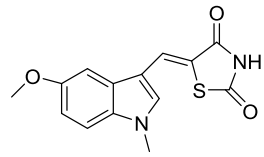
It is well known that adenosine exerts a cytoprotective effect by enhancing the activity of antioxidant enzymes, such as superoxide dismutase (SOD). For this reason, the inhibition of Adenosine Kinase (AK), a catabolic enzyme of adenosine, could be useful for the treatment of oxidative stress in neurological disorders by increasing the levels of endogenous adenosine [514, 515]. In this field, Brogi *et al.* investigated a series of benzoxazine-based structures as dual AK/GSK-3β inhibitors. In particular, compound **110** showed a micromolar activity on both enzymes and, most importantly, proved to be able of preventing ROS formation [516]. Compound **110** was not cytotoxic up to a 50 μM concentration, suggesting that it could be considered an important tool for the treatment of neurodegenerative disorders.



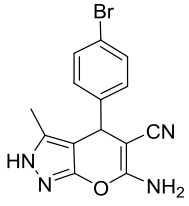
110
GSK-3β = 6.4 μM
AK = 13.6 μM



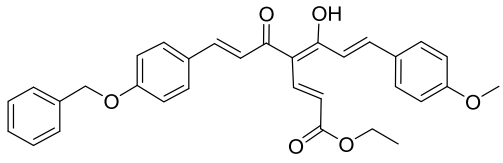
111
GSK-3β = 2.69 μM
HDAC1 = 12.78 μM
HDAC6 = 3.19 μM



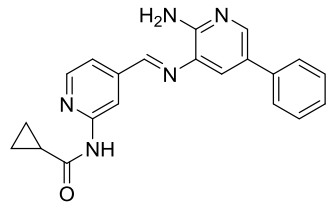
112
GSK-3β = 0.89 μM
Inhib. of τ agg. = 80% at 10 μM



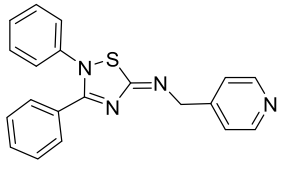
113
GSK-3β = 3.77 μM
NrF2 CD = 9.37 μM



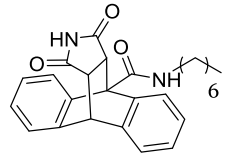
114
GSK-3β = 8.39 μM
Nrf2 inducer in SH-SY5Y cells at 5 μM



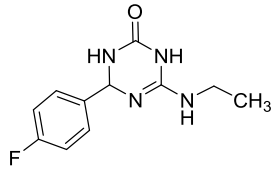
115
GSK-3β = 49 nM
selective Al^{3+}, Cu^{2+} chelator



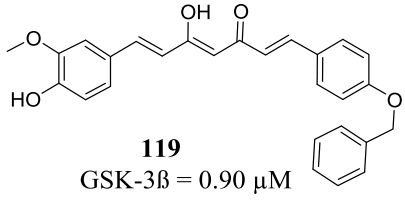
116
GSK-3 = 1.3 μM
PDE-7 = 0.38 μM



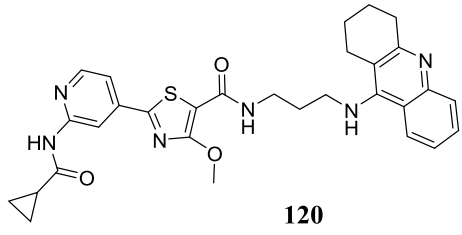
117
GSK-3ß inhib. of 60% at 10 μM
Voltage-gated Ca^{2+} channels = 9 μM



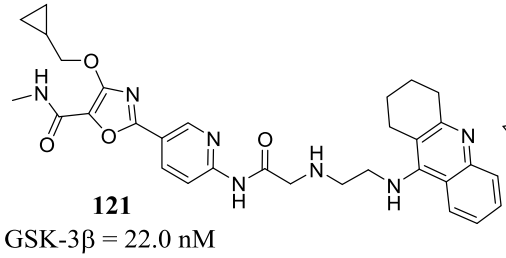
118
GSK-3ß = 7 μM
BACE-1 = 16 μM



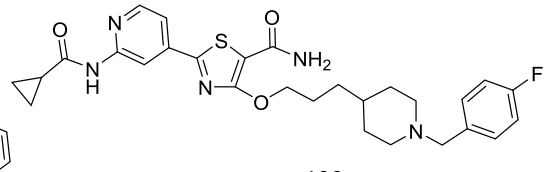
119
GSK-3ß = 0.90 μM
BACE-1 = 0.97 μM



120
GSK-3ß = 66 nM
*h*AchE = 6.4 nM

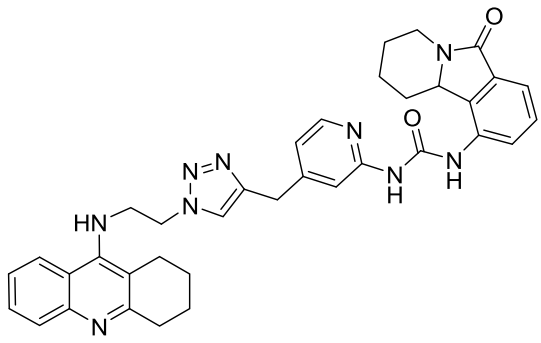


121
GSK-3β = 22.0 nM
*h*AChE = 1.2 nM



122
GSK-3ß = 0.003 μM
*h*AchE = 0.3 μM

Fig. (18). Contd....



123
GSK-3a/b = 7 nM
*h*AChE = 9.5 nM

Fig. (18). Multi-target GSK-3β inhibitors (**110**-**123**). Reported data are IC_{50} values.

5.5.2. Dual GSK-3β/HDAC Inhibitors

Based on the observation that histone deacetylase (HDAC) inhibitors have the potential to reduce memory impairments [517, 518], dual HDAC/GSK-3β inhibitors could be considered attractive multitarget compounds for the treatment of AD. In recent years, several approaches, including virtual screening, have been used for discovering new HDAC/GSK-3β inhibitors [519]. In this field, interesting results have been obtained by De Simone *et al.* [520] who reported promising indole derivatives as neuroprotective agents. In particular, compound **111** is able to induce inhibition of both GSK-3β, HDAC1 and HDAC6 in the micromolar range, with an increase of hystone acetylation and reduction of τ phosphorylation as a result. In addition, compound **111** was found to be nontoxic and protective against oxidative stress in several cell lines, as well as capable of inducing neurogenesis and exhibiting immunomodulatory effects.

5.5.3. Dual GSK-3β/τ Aggregator Inhibitors

Inhibition of hyperphosphorylation of τ protein and formation of neurofibrillary tangles is one of the most actively studied strategy for AD treatment [521]. The thiazolidine derivatives described by Gandini *et al.* proved to be promising dual GSK-3β/τ aggregator inhibitors [522]. In particular, compound **112** was active in the micromolar range on both targets, showing improved cell viability in *in vitro* studies as well as a good membrane permeability in PAMPA assay.

5.5.4. Dual GSK-3β Inhibitors/NrF2 Inducers

There are several experimental observations that NrF2 inducers possess neuroprotective activity in various animal models [523-526]. In this field, several dihydropyranopyrazoles [527] have shown significant anti-inflammatory and neuroprotective activity in *in vitro* studies. In particular, compound **113** (Fig. **18**) proved to be the most promising one. The biological profile of **113** indicates that neuroprotection depends also on NrF2 induction. Moreover, **113** is devoid of neuro- or hepatotoxicity, suggesting it is a good candidate for further studies. Unfortunately, no studies on *in vivo* models of dementia have been performed so far. Recently, another interesting derivative possessing this dual activity has been reported by Di Martino *et al.* [528], who proposed the curcumin derivative **114** as a promising agent for the treatment of Parkinson's disease. Compound **114** showed specific neuroprotective effects in PD pathological events, including neurotoxicity elicited by α-synuclein aggregates and 6-hydroxydopamine, and neuroprotective effects in a *C. elegans* model of PD, thus indicating it as an interesting multitarget agent, valuable to exploit in a multitarget PD perspective.

5.5.5. Dual GSK-3β/Metal Ion Chelator

The GSK-3β inhibitor **115** was designed to chelate metal ions through a 2,3-diaminopyridine moiety while maintaining a good interaction with GSK-3β through the N-(pyridin-2-yl)cyclopropanecarboxamide, able to establish favorable interactions with the hinge region of GSK-3β [529]. **115** is a potent inhibitor with an IC_{50} value of 49 nM, and showed protective effects on learning and memory function in rats with A*β*42-induced AAD, in which **115** increased the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), acetylcholinesterase (AChE), and adenosine

triphosphatase (ATPase) and decreased the concentrations of Aβ42, p-τ, and malondialdehyde (MDA) in the brain tissue [530]. Metal chelators have been proposed for AD treatment as metals, such as copper. are involved in A*β* aggregation, oxidative stress, redox reactions, and A*β*-metal complex production of reactive oxygen species (ROS) [530]. Compound **115** was found to be a highly active GSK-3β inhibitor (IC_{50} = 49 nM), able to chelate Al^{3+} and Cu^{2+}. **115** demonstrate to inhibit Cu^{2+}-induced Aβ42 aggregation, to induce Cu^{2+}-Aβ42 complex disaggregation, to inhibit ROS formation, and to possess antioxidant activity.

5.5.6. Dual GSK-3β/PDE7 Inhibitors

Some 5-imino-1,2,4-thiadiazoles have been reported as dual GSK-3β/PDE7 inhibitors. In particular, compound VP1.14 (**116**) proved to be the most promising agent for the treatment of neurodegenerative disorders [531]. Compound **116** inhibited both enzymes in the nanomolar range and showed neuroprotective and anti-inflammatory activity in *in vitro* and *in vivo* studies.

5.5.7. Dual GSK-3β Inhibitors/Calcium Channel Modulators

Several studies clearly demonstrated that selective calcium channel blockers could reduce the level of Aβ42, improving memory in AD models [532]. For this reason, efforts have been made to develop such dual GSK-3β inhibitors and calcium channel modulators. This research led to the bicyclic maleimide derivative **117**, possessing the dual activity in the micromolar range [533]. Unfortunately, no *in vivo* studies have yet been performed to confirm the efficacy of this compound in AD models.

5.5.8. Dual GSK-3β/5-LO Inhibitors

The role of 5-lypooxygenase (5-LO) in inflammation processes has been demonstrated in the past [534-536]. Taking into account that neuroinflammation is strongly involved in neurodegeneration [537], the development of dual GSK-3β/5-LO inhibitors seems an attractive new approach for the treatment of neurodegenerative disorders. Pergola *et al.* developed a series of indirubine analogs with this dual activity [538]. In particular, 6-BIO (**7**) was active in the micromolar range on both targets, suggesting that this class of compounds may represent a promising strategy for those diseases where both GSK-3 and 5-LO are involved, such as AD.

5.5.9. Dual GSK-3β/BACE-1 Inhibitors

It is widely reported that BACE-1 inhibitors are potentially capable to prevent the aggregation of Aβ42. However, clinical studies showed that this approach did not ameliorate the symptoms in AD patients [539]. For this reason, a multitarget approach involving inhibition of both BACE-1 and GSK-3βmight give better clinical benefits in AD treatment. Prati *et al.* [540, 541] reported a series of 3,4-dihydro-1,3,5-triazin-2(1*H*)-ones as dual GSK-3β/BACE1 inhibitors. The best compound **118** (Fig. **18**) showed neuroprotective activity, no neurotoxicity *in vitro* models, and good brain permeability in mice. For all these reasons, compound **118** can be considered as a good candidate for studies in animal models of AD, and further studies are needed to optimize the structure to obtain a good clinical candidate.

In the same field, De Martino *et al.* [542] developed a series of curcumin analogs with this dual activity. In particular, derivative **119** (Fig. **18**) has been shown to inhibit both targets in the low micromolar concentration range. Furthermore, compound **119** induced NQO1 enzyme, and consequently, it could exert neuroprotective action during oxidative stress. The absence of neurotoxic effects and a fairly good pharmacokinetic profile allow considering compound **119** as a good candidate for further investigation in *in vivo* models of AD.

5.5.10. Dual GSK-3β/AchE Inhibitors

Since low levels of acetylcholine (ACh) lead to cognitive and memory deficits, the recovery of cholinergic function could be considered useful for clinically beneficial [543]. Moreover, it appears that AChE is involved in AD pathogenesis by promoting the formation of Aβ aggregates, suggesting that acetylcholinesterase inhibitors (AChEIs) could affect the metabolic processing of APP and thus influence Aβ42 generation [544, 545]. For all these reasons, multitarget agents endowed with dual GSK-3β/AchE inhibition have been developed. The most representative compounds (**120-123**) of this series are shown in Fig. **18**. All these compounds are hybrid derivatives incorporating substructures of well-known AchE inhibitors such as tacrine (compounds **120**, **121**, **123**) and Donepezil (**122**). Compound **120** showed good inhibition activity both on *h*AchE (IC_{50} = 6.5 nM) and *h*GSK-3β kinase (IC_{50} = 66 nM). Furthermore, **120** showed a good inhibitory effect on *β*-amyloid self-aggregation and on hyperphosphorylation of τ protein in mouse neuroblastoma N2a-τ cells. *in vivo* studies confirmed that **120** significantly improved the cognitive disorders and was less hepatotoxic than tacrine [546]. The same authors reported a similar analog, **121**, capable of inhibiting both targets in the nanomolar concen-

tration range, along with a high kinase selectivity for GSK-3β. The compound also exhibited good permeability across the BBB and the ability to inhibit the phosphorylation of τ protein. Oral administration of **121** exhibited promising cognitive improvement in cognitively deficient mice [547].

The same authors described another derivative with a similar profile, **122**, which was found to be less potent on AchE with respect to GSK-3β (0.3 μM for hAChE and 0.003 μM for hGSK-3β) [548]. Compound **122** exhibited good drug-like properties and showed anti-inflammatory properties at micromolar concentrations, and an interesting neuroprotective profile in an *in vitro* model of oxidative stress-induced neuronal death. **122** also exhibited good permeability across the BBB. Another interesting tacrine-based derivative, **123**, was reported by Oukoloff *et al.* This compound was obtained by a rational design, supported by molecular docking studies performed on AChE and GSK-3. Compound **123**, in the enantiomerically pure form (*R*), inhibits both human AChE and GSK-3α/β in the nanomolar range, exhibits low hepatotoxicity and good BBB penetration without interaction with the P-glycoprotein efflux system [549].

All these approaches indicate the potential use of multitarget agents for the treatment of neurodegenerative disorders, which in some cases have proved to be more effective than the classic polypharmacological approach, avoiding in particular pharmacokinetics side effects due to drug-drug interactions.

CONCLUSION

In this review article, we have briefly summarized the role of the GSK-3β enzyme in neurodegenerative disorders and the efforts made in the last decades for the development of selective GSK-3β inhibitors or multitarget agents as potential candidates for the treatment of these pathologies. The GSK-3β involvement in several signaling pathways related to neuroinflammation, as also in the formation of protein aggregates typical of several neurodegenerative diseases, strongly supports its identification as a therapeutic target for these diseases. As a consequence, the discovery and development of GSK-3β and/or multitarget ligands give rise to attractive tools for the treatment of neuroinflammation and neurodegenerative. Encouraging results were obtained, in fact, some GSK-3β inhibitors (depicted in Fig. **7**) have initiated clinical trials with different applications. In particular, the orphan drug Tideglusib entered in Phase II clinical trials for mild to moderate AD and for PSP where even demonstrating a safe profile, it misses the primary endpoints. A reason for few compounds reaching clinical trials for neurodegenerative disorders despite the plethora of basic research that supports this enzyme as a key therapeutic target could reside in the involvement of GSK-3β in many signaling pathways and into the fact that its action is not peculiar of CNS but it is ubiquitous in our body. Several side effects are still present and efforts should be made in finding inhibitors that selectively act at a central level. For this reason, more detailed pharmacodynamic and ADME/Tox profiles of the reported compounds should be better investigated and considered as a starting point for the search of compounds with an appropriate profile to be considered an ideal drug candidate.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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