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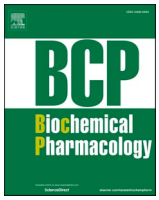

Review

A review of developments in glycogen synthase kinase-3 regulators over the past 10 years

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ABSTRACT

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase that plays a pivotal role in regulating diverse cellular processes. It has been implicated in neurodegenerative diseases, diabetes, mood disorders, and cancer. Over the past few decades, significant progress has been made in developing various types of GSK-3 inhibitors and degradation agents. This review aims to provide a comprehensive overview of the current research landscape of clinical drugs targeting GSK-3, focusing on the structural characteristics and biological functions of GSK-3 inhibitors developed over the past decade. Additionally, it evaluates the advantages, disadvantages, and future trends associated with these different classes of inhibitors. Particular emphasis is placed on compounds currently under clinical evaluation and emerging strategies such as multi-target-directed ligands and proteolysis-targeting chimeras (PROTACs). This article offers valuable insights into the potential of GSK-3 as a therapeutic target.

1. Introduction

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase. Initially, GSK-3 was identified as a regulator (inhibitor) of glycogen synthesis [1]. The active center of GSK-3 is a T-loop structure that binds to threonine through a phosphate-binding pocket containing three key alkaline residues, namely Lys205, Arg96, and Arg180. Thus far, GSK-3 proteins have been shown to have homology in all eukaryotes, and subtypes from distant species, such as flies and humans have more than 90 % homology within the kinase domain [2]. GSK-3 is a kinase with multiple functions in both invertebrate and vertebrate cells. In mammals, there are two subtypes of GSK-3, namely GSK-3α (51 kDa) and GSK-3β (47 kDa), encoded by different genes. GSK-3α and GSK-3β share 85 % overall sequence homology, with 98 % sequence identity in their kinase domains, but only 36 % identity in their carboxyl termini [3]. At the N-terminus, GSK-3α has an additional glycine-rich sequence not present in GSK-3β (Fig. 1). The biochemical properties of the two subtypes are similar, but their functions differ [4]. Research has shown

Abbreviations: GSK-3, Glycogen synthase kinase-3; PROTACs, Proteolysis-targeting chimeras; IR, Insulin receptor; IGF, Insulin-like growth factor; IGFR, Insulin-like growth factor receptor; NF-κB, Nuclear factor kappa B; TGF-β, Transforming growth factor-β; AD, Alzheimer's disease; Aβ, Amyloid beta; sAAPβ, Soluble amyloid precursor protein-beta; APP, Amyloid Precursor Protein; PHFs, Paired Helical Filaments; NFTs, Neurofibrillary Tangles; PS1, Presenilin-1; PKB/Akt, Protein kinase B; PTEN, Phosphatase and Tensin Homolog; AR, Androgen receptor; CCND1, Cyclin D1 gene; FAK, Focal adhesion kinase; MMPs, Matrix metalloproteinases; AP-1, Activating protein-1; TNF-α, Tumor Necrosis Factor-α; IL-6, Interleukin-6; PI3K, Phosphatidylinositol 3-kinase; T2DM, Type 2 diabetes mellitus; SH2, Src-homology 2; IRS-1, Insulin receptor substrate-1; PDK-1, phosphoinositol-dependent kinase-1; PP1, Protein phosphatase 1; DADS, Diallyl disulfide; COX-2, Cyclooxygenase-2; ADME, Absorption, distribution, metabolism, excretion; PK, Pharmacokinetics; FST, Forced Swim Test; TST, Tail Suspension Test; MD, Molecular dynamics; TDZD, Thiadiazolidinone; CDM1, Congenital myotonic dystrophy type 1; SMA, Spinal muscular atrophy; QC, Glutaminyl cyclase; AChE, Acetylcholinesterase; WNT, Wingless-related integration site; TLR4, Toll-like receptor 4; PIP2, Phosphatidylinositol 4,5-bisphosphate; PIP3, Phosphatidylinositol 3,4,5-trisphosphate; Tirap, TIR domain containing adapter protein; Tollip, Toll-interacting protein; MYD88, Myeloid differentiation primary response 88; APC, Adenomatous Polyposis Coli; CREB, cAMP response element-binding protein; PtdIns, phosphatidylinositol; IRS-1, Insulin Receptor Substrate-1; PH, Phosphatase homology; PP1, Protein Phosphatase 1; PtdIns(3,4,5)P_3, Phosphatidylinositol 3,4,5-triphosphate; DYRK1α, Dual-specificity tyrosine-phosphorylation-regulated kinase 1α; DYRK1β, Dual-specificity tyrosine-phosphorylation-regulated kinase 1β; PKA, Protein kinase A; PKC, Protein kinase C.

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that many species contain GSK-3α and GSK-3β, but birds only have GSK-3β. The GSK-3 gene product is highly expressed in the brain. Among them, GSK-3 α is massively expressed in the hippocampus, cerebral cortex, striatum, and cerebellum, while GSK-3β is expressed in almost all brain regions [5].

A large amount of research data indicates that GSK-3 is a pleiotropic enzyme, and more than 100 substrates can be phosphorylated and regulated by GSK-3 [6]. These substrates enable GSK-3 to affect many key cellular functions, such as gene expression, cell structure, neural plasticity, survival, and others as well [7]. Therefore, GSK-3 plays absolutely necessary roles in a diverse range of disorders, such as cancer, neurological diseases, inflammation, and viral infections. Due to the multifunctionality of GSK-3, it can play an indispensable role in regulating the signaling pathways of cellular processes. Here, we summarize the research on GSK-3 over the past 10 years.

2. Overview of GSK-3

GSK-3 is a multifunctional monomeric protein involved in various cellular functions, including differentiation [8], survival [9], glycogen metabolism [10,11], protein synthesis [12], the immune response, and cell death [13]. It is a core component of many pathways, including the insulin/insulin receptor (IR), insulin-like growth factor (IGF)/IGF receptor (IGFR), Wnt/β-catenin, hedgehog, nuclear factor kappa B (NF-κB) [14], and transforming growth factor-β (TGF-β) [15] signaling pathways. To date, approximately 40 proteins involved in numerous cellular processes have been identified as GSK-3β substrates, and more than 500 proteins have been proposed as potential GSK-3β substrates [16]. Therefore, GSK-3 is a key regulatory factor in several diseases.

2.1. The role of GSK-3 in Alzheimer's Disease mechanisms

GSK-3 has been found to play a crucial role in the nervous system and is also an important factor in the pathogenesis of many diseases. In early studies, excessive activity of GSK-3 was found to be one of the causes of progressive neurodegenerative and psychiatric disorders, and the inhibition of GSK-3 was shown to have therapeutic effects. Two isoforms of GSK-3 are present throughout the brain, whereas GSK-3β is found mostly in the cerebral cortex, cerebellum, striatum, hippocampus, and Purkinje cells [17]. Overactive GSK-3 has been found in the brain in Alzheimer's disease (AD) and in some mouse models of AD. The overexpression of GSK-3 *in vivo* induces AD pathology, cognitive impairment, and glial cell proliferation [18–21]. Tau is a recognized substrate for GSK3 [22]. There are many connections between GSK-3 levels and the neuropathological features of AD, and it is a major candidate for Tau protein hyperphosphorylation in AD. GSK-3-mediated phosphorylation of Tau leads to reduced microtubule binding (Fig. 2), which may enhance the formation of paired helices, and may be a prelude to the formation of neurofibrillary tangles [23]. GSK-3 overexpression may also lead to Tau protein hyperphosphorylation and Tau protein deposition found in other neurodegenerative diseases [24]. GSK-3, whose regulatory mechanism is not entirely understood, can be inactivated by phosphorylation by a number of upstream protein kinases such as protein kinase A (PKA), Akt, and protein kinase C (PKC) [25,26]. According to the GSK-3 hypothesis, tau hyperphosphorylation, excessive Aβ production, and its accumulation are all caused by GSK-3 overactivity, which accounts for memory impairment. The function of GSK-3 is influenced by Wnt and insulin signaling. This could be the cause of increased phosphorylation of tau along with subsequent NFT production [27]. Other studies have suggested that changes in GSK-3 activity (such as overactivation or inhibition) can affect emotions, emotional behavior, social skills, and behaviors similar to those seen in schizophrenia [28–34].

2.2. The role of GSK-3 in cancer mechanisms

The tumor-promoting effect of GSK-3β has been reported in various types of cancers. It is closely related to the survival, proliferation, invasion, therapeutic resistance, and stemness of tumor cells [35]. In the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, protein kinase B (PKB, also known as Akt, a serine/threonine kinase downstream of PI3K) can inhibit its activity by phosphorylating the GSK-3β Ser9 site under the stimulation of insulin or other growth factors [36]. GSK-3β has a tumor-inhibitory role. Adiponectin and Phosphatase and Tensin Homolog (PTEN) suppress GSK-3β-mediated β-catenin degradation and cell cycle arrest by inhibiting the PI3K/Akt pathway in prostate tumors and breast cancer (Fig. 3). The deletion of MIF attenuates Akt-dependent GSK-3β phosphorylation and restores the tumor-suppressor activity of GSK-3β in esophageal squamous cell carcinoma. Additionally, GSK-3β phosphorylates various tumor-promoting factors, facilitates their degradation, and prevents them from entering the nucleus [37].

2.3. The role of GSK-3 in inflammation mechanisms

GSK-3β plays an important role in the inflammatory response. GSK-3α inhibition reduces the production of TNF-α, IL-6 and enhances the production of IL-10 in monocytes stimulated by lipopolysaccharide (LPS) [38,39].

PI3K is a lipid kinase that plays an important role in the regulation of various cellular processes involved in the effects of insulin on glycogen metabolism. This kinase is an upstream activator of PKB, which in turn inhibits GSK-3 activity by phosphorylating Ser9, allowing glycogen synthase to dephosphorylate and initiate glycogen synthesis [40], GSK-3 plays an important inhibitory role in the Wnt signaling pathway, and abnormalities in this pathway have been reported to promote the development of degenerative diseases and cancer [41,42], Consistently, phosphorylation of β-catenin by GSK-3 has been shown to disrupt the interaction between β-catenin and NF-κB and promote inflammation. Frizzled receptors are activated by Wnt stimulation to dephosphorylate β-catenin through the cytoplasmic phosphoprotein Disheveled (Fig. 4) [43,44].

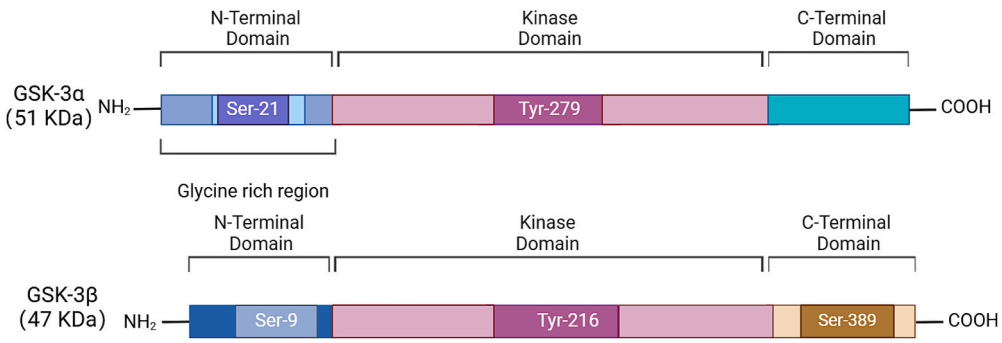


Fig. 1. Schematic representation of mammalian GSK 3α and GSK 3β.

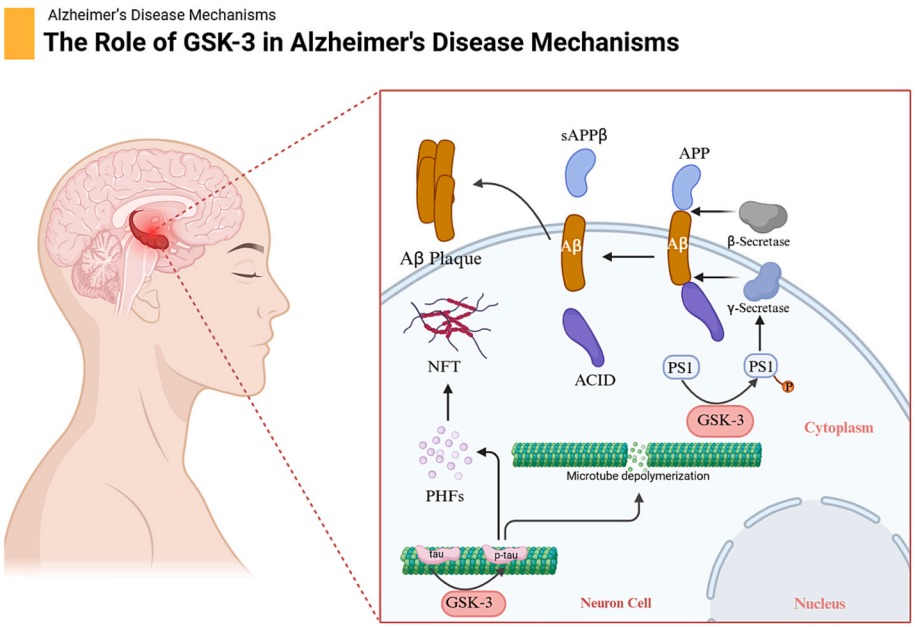


Fig. 2. The role of GSK-3 in Alzheimer's Disease mechanisms. (Aβ: beta-amyloid, sAPPβ: soluble amyloid precursor protein β, PHFs: Paired Helical Filaments, NFT: Neurofibrillary Tangles, PS1: Presenilin-1).

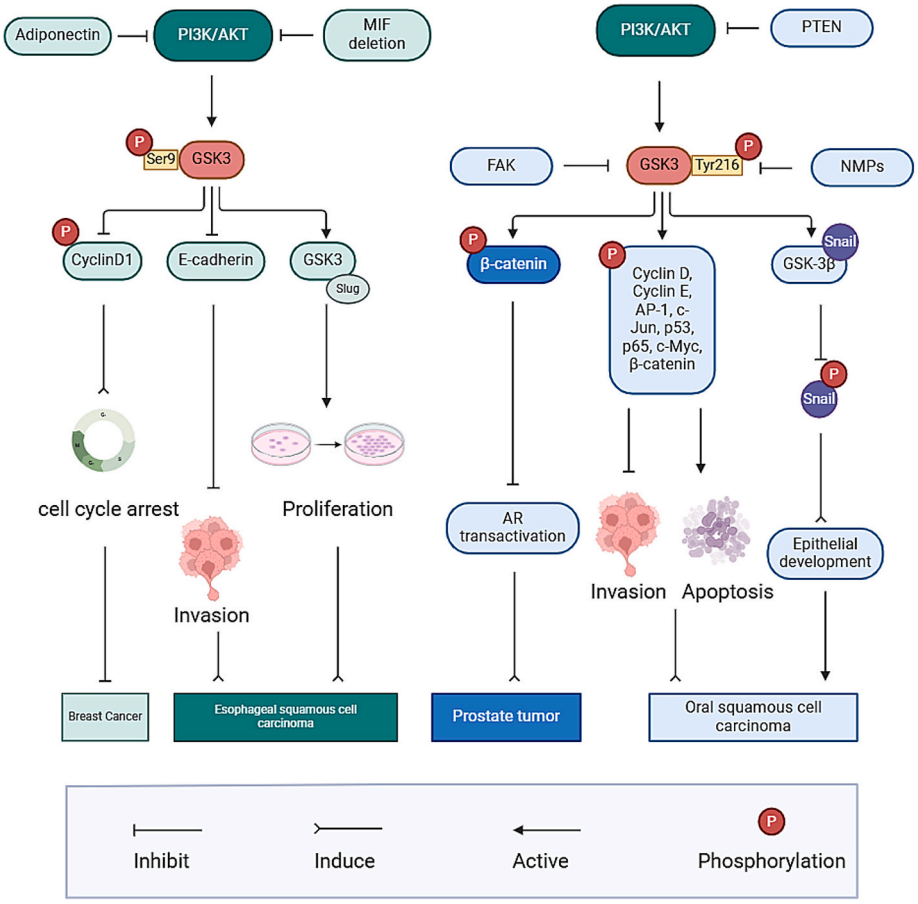


Fig. 3. The role of GSK-3 in cancer mechanisms. (PTEN: phosphatase and tension homolog, AR: androgen receptor, CCND1: cyclin D1 gene, FAK: focal adhesion kinase, MMPs: matrix metalloproteinases, AP-1: activating protein-1).

2.4. The role of GSK-3 in diabetes mechanisms

Insulin resistance is a key factor in the pathogenesis of obesity and Type 2 diabetes mellitus (T2DM) [45]. Numerous studies implicate GSK-3 in the pathogenesis of insulin resistance and T2DM. GSK-3α/β expression and activity are significantly elevated in muscle biopsies of

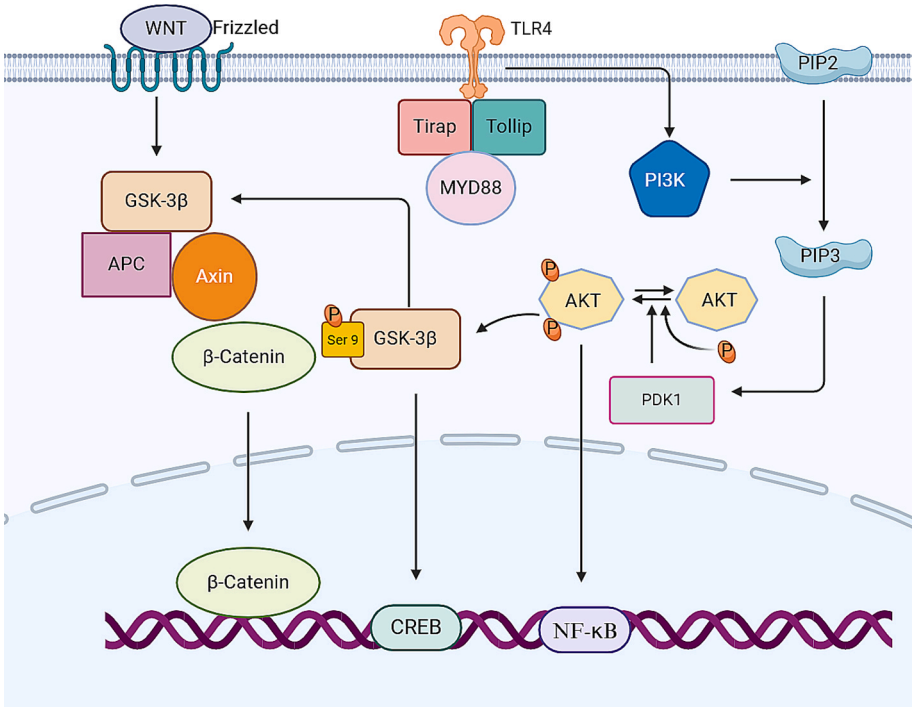


Fig. 4. The role of GSK-3 in inflammation mechanisms. (WNT: Wingless-related integration site, TLR4: Toll-like receptor 4, PIP2: Phosphatidylinositol 4,5-bisphosphate, PIP3: Phosphatidylinositol 3,4,5-trisphosphate, Tirap: TIR–domain-containing adapter protein, Tollip: Toll-interacting protein, MYD88: Myeloid differentiation primary response 88, PI3K: Phosphatidylinositol-3 kinase, APC: Adenomatous Polyposis Coli, PDK1: Phosphoinositide-dependent protein kinase 1, CREB: cAMP response element-binding protein, NF-κB: Nuclear factor-κB).

T2DM patients [46]. Examination of C57B$_1$/6J mice fed a high-fat diet to induce obesity and T2DM, revealed elevated GSK-3 activity in epididymal fat tissue compared with control mice fed a regular chow diet [47]. Some studies have suggested that activation of glycogen synthase may not be impaired in T2DM, rather that the decreased glycogen storage is due to reduced transport [48]. Other studies have suggested that inactivation of GSK-3 is not necessarily affected in insulin resistance and that glycogen synthase activity is affected by other kinases [49,50].

The most thoroughly documented pathway for the inactivation of GSK-3 is in response to insulin and is mediated by PKB, which acts upstream of GSK-3 [36]. Insulin binding to its receptor induces a conformational change in the receptor, resulting in receptor tyrosine kinase activation and the recruitment of Src-homology 2 (SH2) domain–containing proteins, including insulin receptor substrate-1 (IRS-1, Fig. 5) [51]. One of the downstream targets of IRS-1 is the lipid kinase PI3K, which phosphorylates phosphatidylinositol at the 3′-position of the inositol ring to produce phosphatidylinositol 3,4-diphosphate and phosphatidylinositol 3,4,5-triphosphate on the plasma membrane [52]. The accumulation of PtdIns on the plasma membrane leads to the recruitment of proteins containing phosphatase homology (PH) domains, including phosphoinositol-dependent kinase-1 (PDK-1) and PKB [53]. Insulin induces the self-phosphorylation of receptors and the binding of insulin receptor substrate molecules, followed by the recruitment of PI3K to the plasma membrane. Subsequently, phosphatidylinositol 3,4,5-triphosphate (PtdIns(3,4,5)P_3) facilitates signal transduction downstream of PI3K. PKB translocates to the plasma membrane, where it is activated through the phosphorylation of PDK1/2. GSK-3α/β is subsequently phosphorylated and inactivated by PKB, thereby preventing the phosphorylation of downstream substrates, such as glycogen synthase. Glycogen synthase is dephosphorylated and activated by protein phosphatase 1 (PP1).

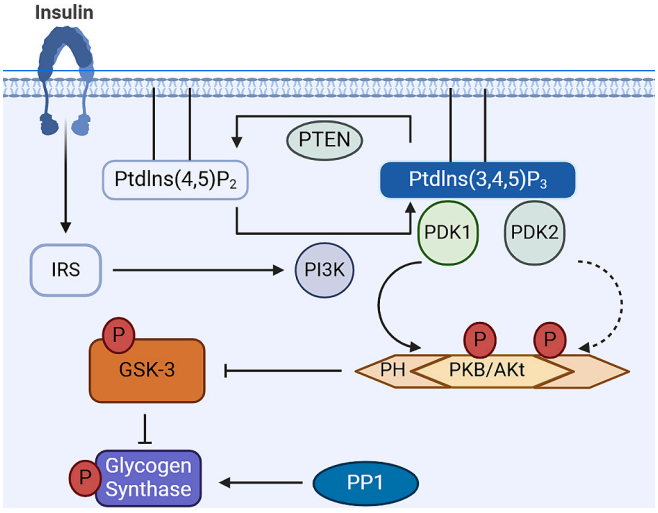


Fig. 5. The role of GSK-3 in Diabetes mechanisms. (IRS: Insulin Receptor Substrate, PtdIns(4,5)P_2: Phosphatidylinositol 4,5-bisphosphate, PtdIns(3,4,5)P_3: Phosphatidylinositol 3,4,5-trisphosphate, PTEN: Phosphatase and Tensin Homolog, PDK1: Phosphoinositide-dependent Protein Kinase 1, PDK2: Phosphoinositide-dependent Protein Kinase, PKB/AKT: Protein Kinase B, PP1: Protein Phosphatase 1).

2.5. Toxicology of GSK-3

GSK-3, a crucial serine/threonine protein kinase in cellular signaling, is a promising therapeutic target for various diseases. However, modulating its activity can lead to significant toxicological effects. Inhibition of GSK-3 may disrupt insulin-mediated glucose metabolism, causing hyperglycemia and abnormal glucose-glycogen homeostasis. As reported in studies like those by Frame and Cohen [54], GSK-3′s role in

normal glucose-glycogen regulation is well-established, and its inhibition can clearly perturb this balance. In the central nervous system, it can increase neuronal excitability, potentially leading to seizures, and cause cognitive deficits related to abnormal tau phosphorylation. Lucas et al [55] demonstrated in their research on GSK-3β conditional transgenic mice that abnormal GSK-3 regulation is associated with such neurological issues. In the heart, aberrant GSK-3 regulation can result in cardiac hypertrophy, arrhythmias, and impaired contractility. Huisamen et al [56] have explored the role of GSK-3β in cardiac function and how its misregulation can lead to these cardiovascular complications. Additionally, GSK-3 inhibition can disrupt the immune response, either causing immunosuppression or over-activation, which may increase the risk of infections. Therefore, careful consideration of these potential adverse effects is essential, and more selective approaches to modulate GSK-3 activity are needed.

3. Clinical evaluation of GSK-3 inhibitors and Proteolysis-Targeting chimeras

Sixty-three GSK-3 inhibitors have been or are currently in the clinical development stage for the treatment of different diseases, but only 40 structures of small molecule GSK-3 inhibitors are publicly available (Table 1). (https://synapse.zhihuiya.com/) (https://clinicaltrials.gov/).

In addition, among these 40 published inhibitors, those targeting AD account for 41 %, followed by nervous system diseases, bipolar and related disorders, cancer, diabetes, and other indications (Fig. 6).

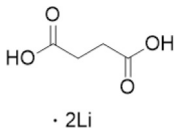
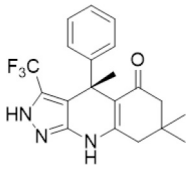
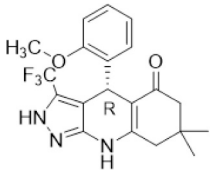
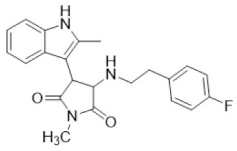
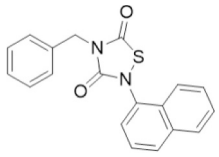
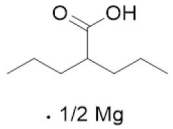
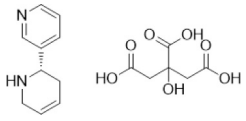
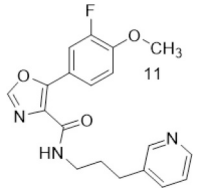
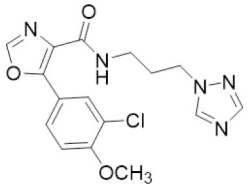
GSK-3 inhibitors have been used to treat a wide range of neurological diseases, including AD, highlighting the importance of GSK-3 inhibitors in neurological diseases. It is clear to see that the field of GSK-3 inhibitors is very broad. The research and development of GSK-3 inhibitors are steadily advancing, with two compounds approved for the market, providing impetus for the advancement of these drugs. Forty-three (66.7 %) GSK-3 inhibitors are at the preclinical stage, indicating that the design and synthesis of GSK-3 inhibitors have become increasingly mature. This also highlights the widespread attention paid to GSK-3 inhibitors. Lithium succinate (**1**) and magnesium valproate (**6**) have been approved for treating seborrheic dermatitis and epilepsy, respectively. Elraglusib (**21**) and anatabine citrate (**7**) have entered phase II clinical trials and have been used to treat AD and bone metastases, respectively. ARA-014418 (**30**), AZD-2858 (**32**), LY-2090314 (**33**), tideglusib (**5**), and AZD-1080 (**36**) were terminated in clinical trials; LY-2090314 (**31**) was terminated in phase II; and tideglusib (**5**) was terminated in phase III. The other drugs are in the preclinical or drug-discovery stages. Few drugs have entered the late stages of clinical development, and most have been discontinued in clinical trials, mainly because of their strong toxic side effects. Therefore, the development of GSK-3 inhibitors with reduced toxic side effects is a top priority [91].

4. GSK-3 Inhibitors as a therapeutic target for treatment of human diseases

4.1. Natural products

Turmeric (*Curcuma longa*) contains an active ingredient called curcumin **(41**, Researchers use CLC drug discovery workbench for preparing curcumin), which has shown promising therapeutic properties against various diseases. The prediction from in silico analysis results indicated that curcumin conjugates have good binding affinity with the stem cell target protein, human GSK-3β [92]. The activity of GSK-3β is determined by the phosphorylation of Ser9 and Tyr216 sites. The Tyr216 site can be phosphorylated through autophosphorylation, and there are also studies reporting that Src family tyrosine kinases can phosphorylate it. After phosphorylation, GSK-3β is constitutively activated. At this time, it can phosphorylate substrates, participate in cell proliferation, cell survival, gene expression, neural development, and many other cellular activities, and is also related to cancer, diabetes, neurodegenerative diseases, and other pathological processes. Phosphorylation at the Ser9 site leads to inactivation of GSK-3β. After Ser9 phosphorylation, it binds to the pre-phosphorylation pocket of the substrate-binding region, reducing its affinity for substrate binding and thereby inhibiting GSK-3β kinase activity. For example, the P-GSK-3β Ser9 protein levels in mice treated with berberine (42, Wuhan Bid-Winning Technology Co., Ltd., Wuhan, China) are significantly reduced, leading to GSK-3β inhibition [93]. Meridianins A (**43**, University of Barcelona, Barcelona, Spain) and lignarenone B (**44**, University of Barcelona, Barcelona, Spain) inhibit the activity of GSK-3β, possibly through ATP-competitive and non-competitive allosteric mechanisms. In addition, these molecules from marine sources promote the growth of neural processes in primary cortical neurons without inducing neurotoxicity [94]. Pannorin (**45**, purified from the extract of the fermentation), alternariol (**46**, obtained from the mycelium extract), and alternariol-9-methyl ether (**47**, obtained from the mycelium extract) show weak toxic activity against microorganisms and human cells. Significantly, they exhibit significant inhibitory effects against GSK-3 kinase, with IC_{50} values of 0.13 ± 0.04 μM, 0.20 ± 0.02 μM, and 0.35 ± 0.04 μM. These experiments are of great significance for elucidating compounds as promising candidate drugs. Compounds **45**–**47** all have a highly oxidizable and electron-rich benzocoumarin as their core structure. This makes it easy for researchers to speculate that this may constitute a privileged structural feature for GSK inhibition. The lactone functionality may serve as an electrophilic warhead for the covalent inhibition of this target [95]. The naturally halogenated indirubin (**48**, Cayman Chemical/Biomol, Hamburg, Germany), 6-bromoindirubin (**49**, Cayman Chemical/Biomol, Hamburg, Germany), has selective and strong inhibitory activity against mammalian GSK-3β (IC_{50}: 0.01 – 0.1 μM). 6BIO (**50**, Cayman Chemical/Biomol, Hamburg, Germany) showed significantly enhanced inhibitory activity against GSK-3 after replacing the carbonyl groups of compound **49** with oxime hydroxyl groups, indicating that the interaction between oxime hydroxyl groups played an important role in stabilizing the binding modes of these structures [96]. The alkaloid hymenialdisine (**51**, isolated and purified) is a known metabolite that was isolated for the first time in the 1980 s from *Hymeniacidon Aldis*, *Axinella verrucosa*, and *Acanthella aurantiaca*. It demonstrates a strong inhibitory effect against GSK-3 kinase at 10 nM. Western blotting analysis has confirmed that geduin (**52**, isolated and purified) has a certain inhibitory effect against GSK-3β and a protective effect against neuroblastoma, but the specific inhibitory data still need further clarification [97]. Psoralidin (**53**, TargetMol Chemicals Inc. Boston, Massachusetts, USA) and Romanic acid (**54**, MedChemexpress, State of New Jersey, USA) in more than 70 natural products were found to have inhibitory effects against GSK-3 kinase. Molecular docking results also showed that compounds **53** and **54** have good affinity for GSK-3 at eight sites [98]. Twenty-one known Amaryllidaceae alkaloids of various structural types, one undescribed alkaloid, narcimatuline, and compounds caranine (**55**, isolated and purified), masonine (**56**, isolated and purified), and narimatuline (**57**, isolated and purified) all exhibit GSK-3 kinase inhibitory activity [99]. Tricetin (**58**, Extrasynthese, Genay, France) suppresses the migration and presenilin-1 expression of nasopharyngeal carcinoma through the Akt/GSK-3β pathway, and increases the phosphorylation of the Ser9 site of GSK-3, leading to GSK-3 inactivation. However, the specific inhibitory activity of tricetin compound **58** against GSK-3 needs further evaluation [100]. The chemopreventive effects of garlic may be attributed to the anti-inflammatory properties of its sulfur-containing constituents, including diallyl disulfide (DADS) (**59**, Sigma, Livonia, Michigan, USA). DADS inhibits the expression of GSK-3β *in vitro* and upregulates the Ser9 phosphorylation of GSK-3β, while DADS-mediated inhibition of NF-kB and COX-2 is GSK-3β dependent. *In vivo*, further confirmation has been provided for the inhibitory effect of DADS against GSK-3β [101]. Schisandrin B stereoisomers **60** (isolated and purified) and **61** (isolated and purified) have IC_{50} values of 81 and 73 nM, respectively (Fig. 7). They can alleviate antibody-induced cell damage and cognitive impairment in mice with

Table 1
Inhibitors already in the clinical stage and preclinical stage for GSK-3.

Drug	Structure	Highest research and development stage/ target/	Adaptation indications under study	Original research institution and country	Reference
Lithium succinate (**1**)		Approved for listing Gsk-3β IMPA1MGluR3	nervous system disease	ScotiaCanada	[57]
BRD-1652 (**2**)		Preclinical GSK-3	Mood Disorders	Harvard Medical School; Massachusetts, United States	[58]
ML320 (**3**)		PreclinicalGSK-3β	Alzheimer Disease Bipolar and related disorderscardiac hypertrophy	The Broad Institute, Inc. Massachusetts, United States	[58]
IM-12 (**4**)		PreclinicalGSK-3β	Alzheimer Disease	Universität RostockGermany	[59]
Tideglusib (**5**)		Clinical Phase IIIGSK-3β	Alzheimer Disease	Noscira SASpain	[60]
Magmesium Valproate (**6**)		Approved for listing Gaba transaminase × Gsk-3	Epilepsy	Hunan Xiangzhong Pharmaceutical Co., Ltd.China	[61]
Anatabine citrate (**7**)		Clinical Phase II AChR APP GSK-3βNF-κB	Alzheimer Disease	Rock Creek Pharmaceuticals, Inc. Virginia, United States	[62]
[11C]OCM-44 (**8**)		PreclinicalGSK-3β	Alzheimer Disease	Pfizer Inc.New York, United States	[63]
11C-PF-367 (**9**)		PreclinicalGSK-3	Nervous system disease	Pfizer Inc.New York, United States	[64]

(*continued on next page*)

Table 1 (*continued*)

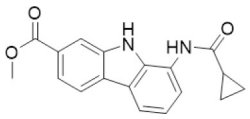
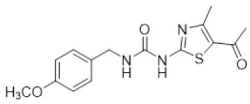
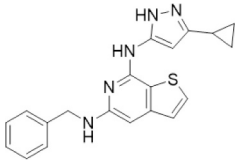
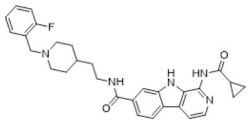
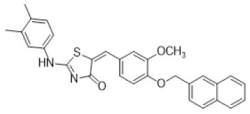
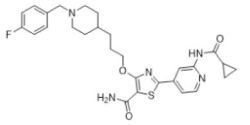
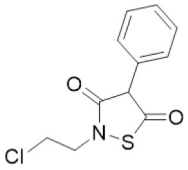
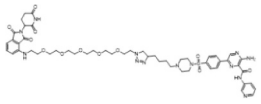
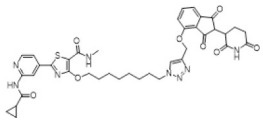
Drug	Structure	Highest research and development stage/ target/	Adaptation indications under study	Original research institution and country	Reference
ZDWX-25 (**10**)		Preclinical DYRK1A x GSK-3β	Alzheimer Disease	Shenyang Pharmaceutical UniversityLiaoning Province, China	[65]
VP2.51 (**11**)		PreclinicalGSK-3α	Motor Neuron Disease	Universidad Complutense de MadridSpain	[66]
ARN25068 (**12**)		Preclinical D YRK1A x FYN x GSK-3β	Alzheimer Disease	Istituto Italiano di TecnologiaItaly	[67]
ZLWH-23 (**13**)		Preclinical AChE x GSK-3β	Alzheimer Disease	Shenyang Pharmaceutical UniversityLiaoning Province, China	[68]
ZINC09036109 (**14**)		PreclinicalGSK-3β	Alzheimer Disease	Central University of RajasthanIndia	[69]
GD29 (**15**)		Preclinical AChE x GSK-3β	Alzheimer Disease	China Pharmaceutical UniversityJiangsu Province, China	[70]
KRM-189 (**16**)		PreclinicalGSK-3β	Bipolar and Related Disorders; Diabetes Mellitus, Type 2; Inflammation	Korea Research Institute of Chemical TechnologyDaejeon, South Korea	[71]
PT-65 (**17**)		PreclinicalGSK-3β	Alzheimer Disease	China Pharmaceutical UniversityJiangsu Province, China	[72]
PG-21 (**18**)		PreclinicalGSK-3β	Neurodegenerative Diseases	VBI Vaccines, Inc.Massachusetts, United States	[73]
FX-345	Unpublished	Clinical Phase IIGSK-3	Neurogenic hearing loss	Frequency Therapeutics, Inc. Massachusetts, United States	*
IB-AD	Unpublished	PreclinicalGSK-3β	Alzheimer Disease	Incyte Corp.Delaware, United States	*
GSK-3β targeting therapy	Unpublished	Drug discoveryGSK-3β	Nervous System Diseases	Angelini Pharmaceuticals Romania SRLRomania	*
4MT-01 series	Unpublished	PreclinicalGSK-3β	Alzheimer Disease	4 M Therapeutics, Inc.New Jersey, United States	*
4MT-A	Unpublished	PreclinicalGSK-3β	Bipolar and Related Disorders; Mania	4 M Therapeutics, Inc.New Jersey, United States	*
4MT-B	Unpublished	PreclinicalGSK-3β	Bipolar and Related Disorders; Mania	4 M Therapeutics, Inc.New Jersey, United States	*
4MT2001	Unpublished	PreclinicalGSK-3β	Bipolar and Related Disorders; Central Nervous System Diseases	4 M Therapeutics, Inc.New Jersey, United States	*

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Table 1 (*continued*)

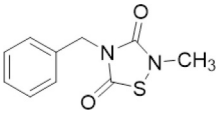
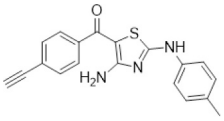
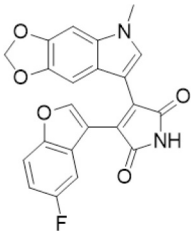
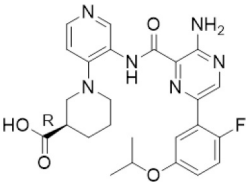
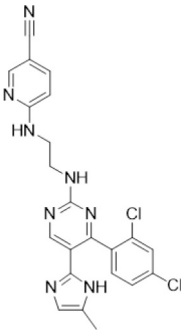
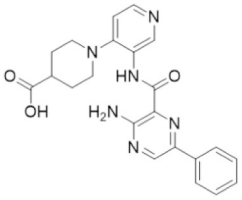
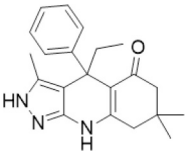
Drug	Structure	Highest research and development stage/ target/	Adaptation indications under study	Original research institution and country	Reference
KWLZ-9e	Unpublished	PreclinicalGSK-3β	Alzheimer Disease	China Pharmaceutical UniversityJiangsu Province, China	*
NTX-721	Unpublished	Preclinical GSK-3β x Sp1	Alzheimer Disease; Brain Injuries, Traumatic; Huntington Disease	NeuroTau, Inc.Tennessee, United States	*
TDZD-8 (**19**)		PreclinicalGSK-3β	Leukemia	University of RochesterNew York, United States	[74]
ABC-1183 (**20**)		Preclinical CDK9 GSK-3αGSK-3β	Neoplasms	Apogee Biotechnology Corp. Pennsylvania, United States	[75]
Elraglusib (**21**)		Clinical Phase II GSK-3β	Bone metastases	University of IllinoisIllinois, United States	[76]
PPRX-1701	Unpublished	Preclinical GSK-3 x JAK2	Glioblastoma	The Brigham & Women's Hospital, Inc.Massachusetts, United States	*
GNF-4877 (**22**)		Preclinical DYRK1A × GSK-3β	Diabetes	Novartis AGSwitzerland	[77]
CHIR-911 (**23**)		PreclinicalGSK-3	Diabetes	Novartis Institutes for Biomedical Research, Inc.Massachusetts, United States	[78]
GNF-7156 (**24**)		Preclinical DYRK1A x GSK-3β	Diabetes	Novartis AGSwitzerland	[77]
BRD-0705 (**25**)		Preclinical GSK-3α	Hemic and Lymphatic Diseases	Dana-Farber Cancer Institute, Inc; Massachusetts, United States	[79]

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Table 1 (*continued*)

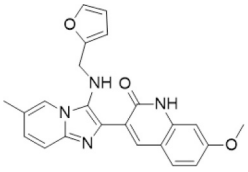
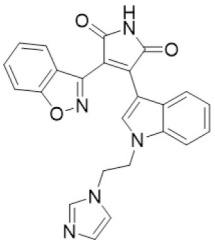
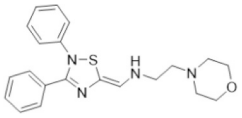
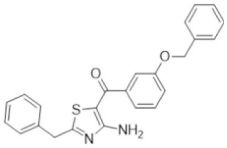
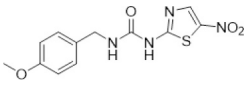
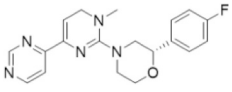
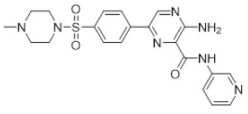
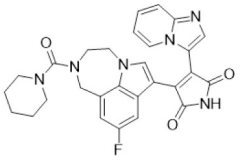
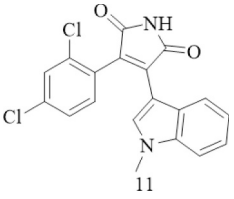
Drug	Structure	Highest research and development stage/ target/	Adaptation indications under study	Original research institution and country	Reference
BCN-057 (**26**)		PreclinicalGSK-3β	Radiation Injuries	University of California, Los AngelesCalifornia, United States	[80]
YQ138 (**27**)		PreclinicalGSK-3β	Brain Ischemia	China Pharmaceutical UniversityJiangsu Province, China	[81]
VP3.15 (**28**)		Preclinical GSK-3 x PDE7	Retinitis Pigmentosa	Consejo Superior de Investigaciones CientíficasSpain	[82]
T-1686568	Unpublished	Drug discoveryGSK-3β	COVID-19	University of British ColumbiaCanada	*
NNC-570558 (**29**)		PreclinicalGSK-3	–	Novo Nordisk A/SDenmark	WO2001056567A1
ARA-014418 (**30**)		PreclinicalGSK-3	–	AstraZeneca PLCUnited Kingdom	[83]
SAR-502250 (**31**)		Drug discovery GSK-3βTau tubulin kinase family	–	Sanofi SAFrance	[84]
AZD-2858 (**32**)		PreclinicalGSK-3	–	AstraZeneca PLCUnited Kingdom	[85]
LY-2090314 (**33**)		Clinical Phase IIGSK-3	–	Eli Lilly & Co.Indiana, United States	[86]
[11C]SB-216763 (**34**)		PreclinicalGSK-3	–	Indiana UniversityIndiana, United States	[87]

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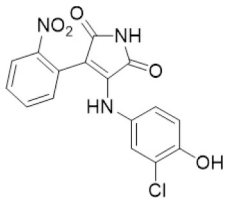
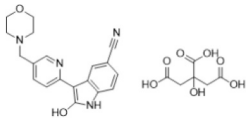
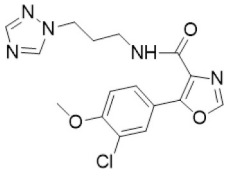
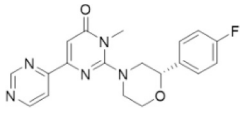
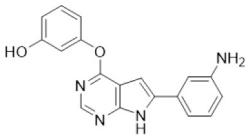
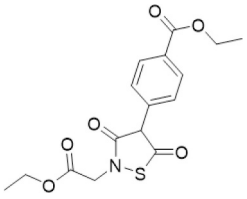
Table 1 (*continued*)

Drug	Structure	Highest research and development stage/ target/	Adaptation indications under study	Original research institution and country	Reference
SB-415286 (**35**)		Preclinical GSK-3	–	University of OklahomaOklahoma, United States	[88]
AZD-1080 (**36**)		Clinical Phase IGSK-3β	–	AstraZeneca Pharmaceuticals Co. Ltd.Jiangsu Province, China	[89]
PF-04802367 (**37**)		Drug discovery GSK-3	–	Pfizer Inc.New York, United States	[64]
SAR-502250 (**38**)		Drug discovery GSK-3β x Tau tubulin kinase (TTBK) family	–	Sanofi SAFrance	[84]
TWS-119 (**39**)		PreclinicalGSK-3β	–	The Scripps Research InstituteCalifornia, United States	[90]
KRM-191 (**40**)		PreclinicalGSK-3β	–	Korea Research Institute of Chemical TechnologyDaejeon, South Korea	[71]
DM 204	Unpublished	Preclinical B2 receptorGSK-3β	–	DiaMedica Therapeutics, Inc. Minnesota, United States	*
Neu-120	Unpublished	Clinical Phase I/II GSK-3β MAO-BNMDA receptor	–	Neurim Pharmaceuticals Ltd. Israel	*
AF-3581	Unpublished	Drug discoveryGSK-3β	–	Angelini Pharma, Inc.Georgia, United States	*
CP-70949	Unpublished	Drug discoveryGSK-3β	–	Pfizer Inc.New York, United States	*
DM-204	Unpublished	Drug discovery B2 receptorGSK-3β	–	DiaMedica Therapeutics, Inc. Minnesota, United States	*
Glycogen Synthase Kinase-3 Inhibitors	Unpublished	Drug discoveryGSK-3	–	Boehringer Ingelheim International GmbHGermany	*
JGK-263	Unpublished	Drug discoveryGSK-3β	–	Jeil Pharmaceutical Co., Ltd. Seoul, South Korea	*
LY-GSK-3i	Unpublished	Drug discoveryGSK-3	–	Eli Lilly & Co.Indiana, United States	*
NP-103	Unpublished	Drug discoveryGSK-3	–	Noscira SASpain	*
VX-608	Unpublished	PreclinicalGSK-3β	–	Vertex Pharmaceuticals, Inc. Massachusetts, United States	*
ARN24161	Unpublished	Preclinical DRDs x GSK-3β	–	Nxera Pharma UK Ltd.United Kingdom	*

*: The data comes from https://synapse.zhihuiya.com/ and https://clinicaltrials.gov/.

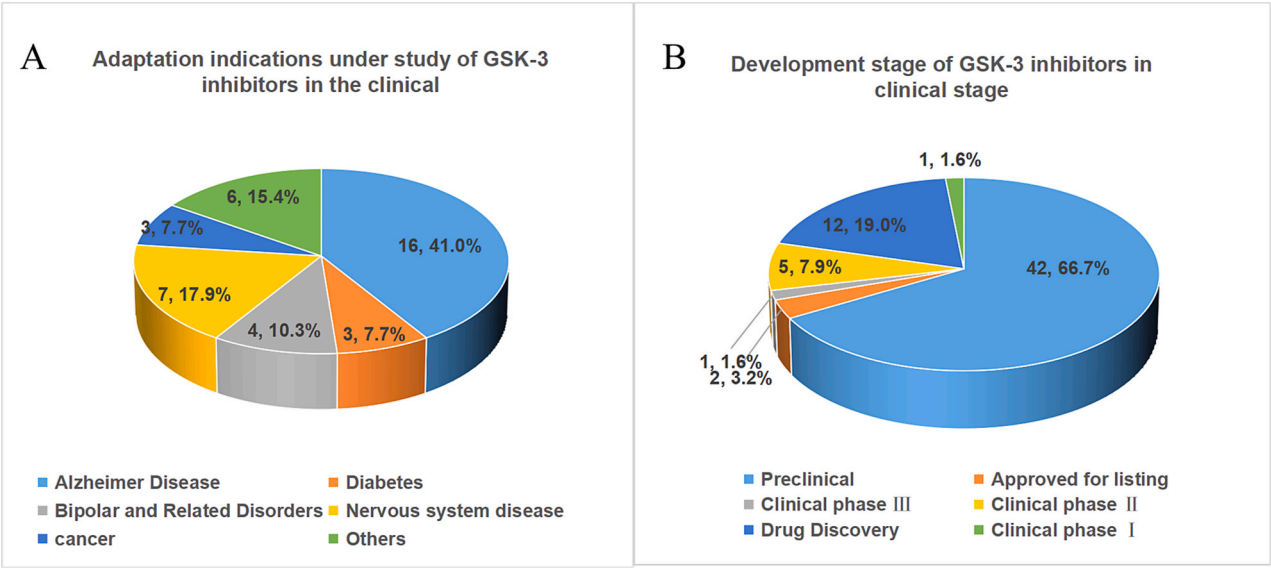


Fig. 6. (A) Adaptation indications under study of GSK-3 inhibitors in the clinical, (B) Development stage of GSK-3 inhibitors in clinical stage.

AD [102].

4.2. ATP competitive inhibitor

ATP-competitive inhibitors are the most widely studied GSK-3 inhibitors. They mainly act by inhibiting GSK-3 through competition with ATP for binding to ATP-binding sites. ATP-competitive inhibitors of GSK-3 generally have strong activity, reaching single-digit nanomolar or even picomolar levels. This type of inhibitor 1) has a low molecular weight; 2) has a planar hydrophobic heterocyclic structure; and 3) binds to protein kinases through hydrophobic interactions and hydrogen bonding. When interacting with inhibitors, Val135 of GSK-3β acts as both a donor and acceptor of hydrogen bonds, while Asp133 acts as an acceptor of hydrogen bonds. There are also many types of ATP-competitive inhibitors, which are introduced in the following sections.

4.2.1. Benzimidazole, Benzopyrazole, and pyrazole scaffold GSK-3 inhibitors

Compounds **62** and **63**, synthesized on the basis of structural modification of the GSK-3 inhibitor ARA-014418 (**30**), have a certain inhibitory effect against GSK-3 (IC_{50}: 86 ± 23 nM and 130 ± 60 nM, respectively), but their effects are not as great as that of compound **30** (GSK-3β IC_{50} = 104 nM) [103]. Compound **64** (4 nM) has good inhibitory activity against GSK-3 kinase and shows superiority in the treatment of central nervous system disorders (Fig. 8). Although compound **65** (72 nM) had less inhibitory effect than compound **64** against GSK-3 kinase, its absorption, distribution, metabolism, and excretion (ADME) properties are improved [104]. Compound **66** exhibits good GSK-3β kinase inhibitory activity, reduced hERG activity, good *in vitro* ADME properties, and good kinase selectivity. Although its exposure level was low, compound **66** demonstrated efficacy and complete reversal of amphetamine overdose in an *in vivo* therapeutic model of mania, without a sedative effect [105]. Compound **65** has a chiral carbon, and its activity against GSK-3 kinase has been tested in both *R* and *S* configurations. Compound **67**, which is in the *S* configuration, has the best kinase activity against GSK-3 (GSK-3α IC_{50}: 0.10 ± 0.001 nM; GSK-3β IC_{50}: 0.13 ± 0.03 nM). The racemic mixture has good oral bioavailability and significantly reduces Tau protein phosphorylation in an AD model [106]. We attempted to perform molecular docking of compound **67** (PDB: 8DJC), which exhibited the best activity among the benzimidazole and benzopyrazole scaffolds (Fig. 9). Molecular docking results showed that compound **67** was perfectly embedded into this pocket, and the sp^2 nitrogen of the pyridine moiety formed a hydrogen bond with the Lys85 amine (2.88 Å). The 2-methylmorpholine group occupies the ribose-binding site and engages in favorable hydrophobic interactions with the protein, resulting in enhanced potency. Among a series of spiro [5.5] undeca-ring compounds, compound **68** was shown to have a significant inhibitory effect and selectivity towards other kinases. Compounds **69** and **70** also exhibit good GSK-3 inhibitory activity [107]. Novel treatments for bipolar disorder with improved efficacy and a broader spectrum of activity are urgently needed. GSK-3β has been suggested to be a key player in the pathophysiology of bipolar disorders [17,108]. Among the compounds assessed *in vivo* pharmacokinetics (PK) experiments, intraperitoneal dosing of compound **71** showed an encouraging plasma PK profile and brain exposure, as well as efficacy, in a mouse model of mania [109]. A series of 4,5-disubstituted aminopyrazole derivatives have been developed as a novel class of multifunctional GSK-3β inhibitors. Five bisindolyl-substituted aminopyrazoles (**72**, **73**, **74**, **75**, and **76**) possess potent GSK-3β inhibitory activities with suppressive effects against glial inflammation and oxidative neurotoxicity. In addition, compound **74** significantly reduces microglial activation and astrocyte proliferation in the brains of LPS-injected mice, showing potent *in vivo* anti-inflammatory effects [110]. Compound **77** has the strongest selectivity and was found to be highly selective against a panel of 124 human protein kinases. Molecular modeling has also shown that, despite overall conservation in sequence and conformation between the three protein kinases (HsGSK3β, HsCDK2, and TbGSK3), the binding pockets have distinct features that determine their specificity for particular compounds [111].

4.2.2. Oxadiazole scaffold

Compounds **78** and **79** are derivatives of oxadiazole, and they exhibit good inhibitory effects against GSK-3α and GSK-3β (Fig. 10). Among them, compound **78** exhibits significant inhibitory effects against GSK-3α (2 nM) and GSK-3β (17 nM). Although the inhibitory effect of compound **79** (GSK-3α: 3.5 nM; GSK-3β: 96.6 nM) against GSK-3 is not as good as that of compound **78**, compound **79** has better selectivity [112]. We performed molecular docking on compound **78** (PDB: 3F88), which exhibited the best activity among the benzimidazole and benzopyrazole scaffolds (Fig. 11). The results showed that compound **78** was completely embedded in the pocket, and the biphenyl system interacted with Cys199, Met101, Leu132, and Val110, firmly occupying the hydrophobic part of the protein pocket. The hydrophobic nitrile group of compound **78** may enhance its activity, and the nitrogen in the pyridine

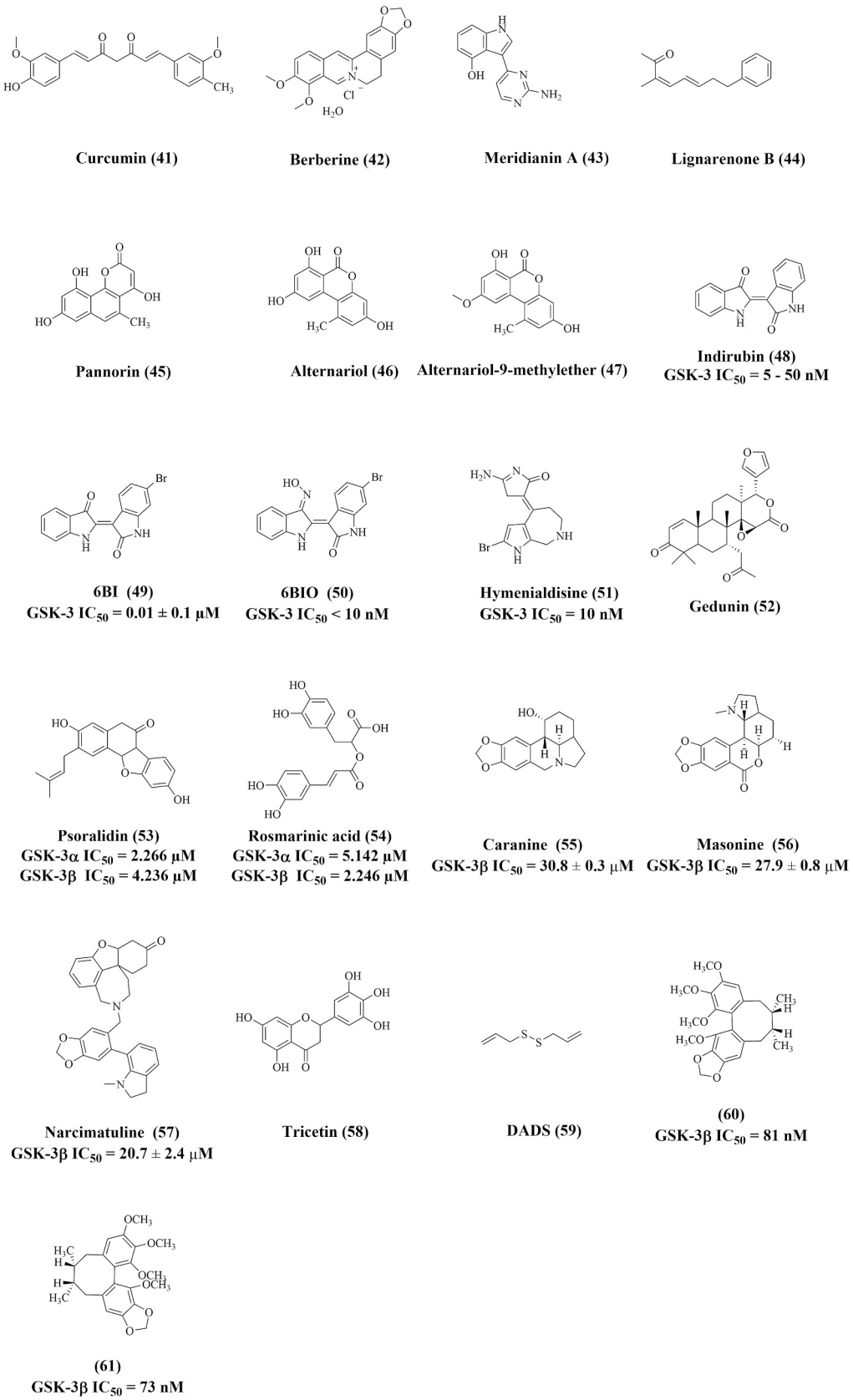
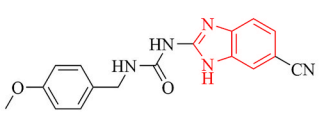
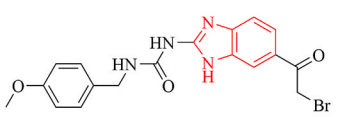


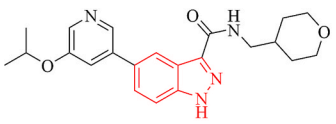
Fig. 7. Natural GSK-3 inhibitors.



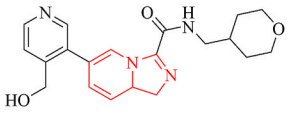
62
GSK-3 IC_{50} = 86 ± 23 nM



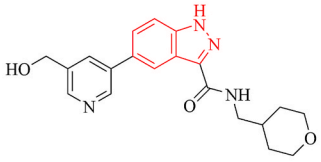
63
GSK-3 IC_{50} = 130 ± 60 nM



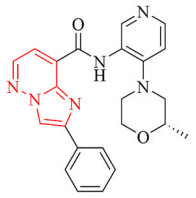
64
GSK-3β IC_{50} = 4 nM



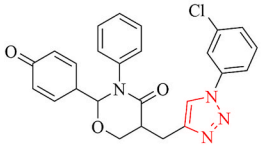
65
GSK-3β IC_{50} = 72 nM



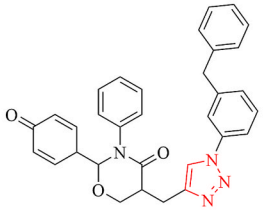
66
GSK-3β IC_{50} = 4 nM



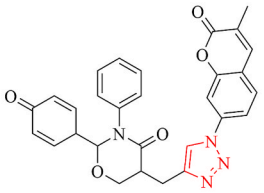
67
GSK-3α IC_{50} = 0.10 ± 0.01 nM
GSK-3β IC_{50} = 0.13 ± 0.03 nM



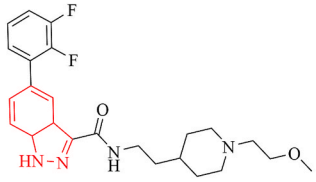
68
GSK-3α IC_{50} = 7.04 μM



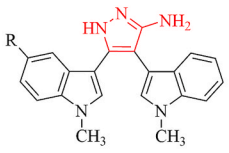
69
GSK-3β IC_{50} = 1.53 μM



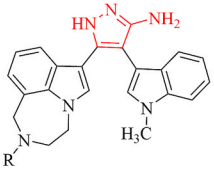
70
GSK-3β IC_{50} = 11.4 μM



71
GSK-3β IC_{50} = 18 nM

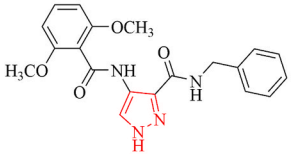


72 R = F GSK-3β IC_{50} = 1.28 ± 0.18 nM
73 R = Br GSK-3β IC_{50} = 1.93 ± 0.22 nM
74 R = OCH_3 GSK-3β IC_{50} = 1.76 ± 0.19 nM



75 GSK-3β R =  **IC_{50} = 1.46 ± 0.04 nM**

76 GSK-3β R = H IC_{50} = 1.48 ± 0.30 nM



77
GSK-3β IC_{50} = 1 nM

Fig. 8. Benzimidazole, benzopyrazole, and pyrazole scaffold GSK-3 inhibitors (All compounds are derived from syntheses carried out by the aforementioned researchers).

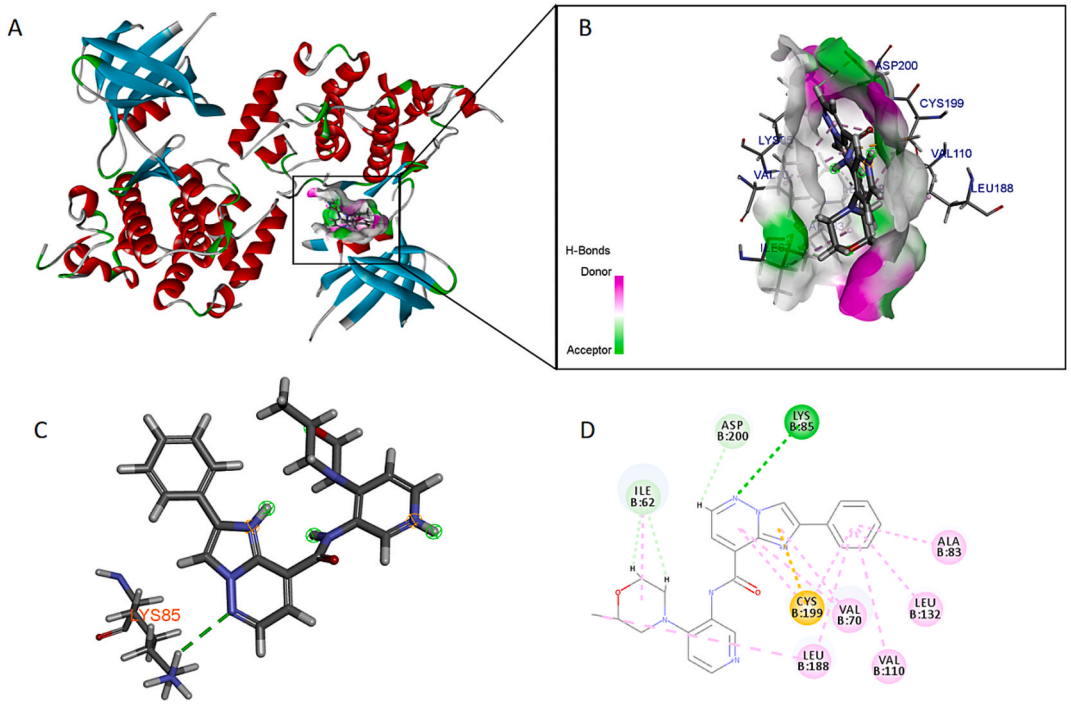
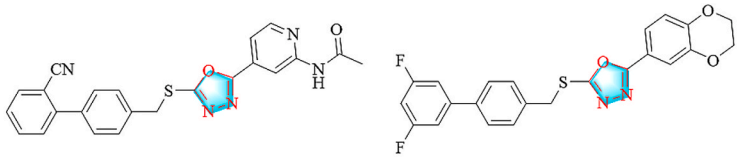
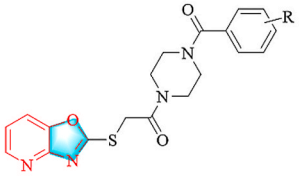


Fig. 9. (A) Docking model of compound **67** and GSK-3 (PDB: 8DJC). (B) Docking model of compound **67** and GSK-3 kinase in the active pocket. (C) Compound **67** forms a three-dimensional interaction with Lys85 through hydrogen bonding. (D) 2D docking model of compound **67** and GSK-3.

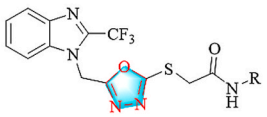


78
GSK-3α IC_{50} = 2 nM
GSK-3β IC_{50} = 17 nM

79
GSK-3α IC_{50} = 3.50 nM
GSK-3α IC_{50} = 96.6 nM



80 R = 4-NO_2 GSK-3β IC_{50} = 0.53 ± 0.03 μM
81 R = 4-Cl GSK-3β IC_{50} = 0.34 ± 0.02 μM
82 R = 2-CH_3 GSK-3β IC_{50} = 0.39 ± 0.03 μM
83 R = 4-CH_3 GSK-3β IC_{50} = 0.47 ± 0.05 μM



84 R = Phenyl GSK-3β IC_{50} = 0.13 ± 0.01 μM
85 R = 4-Methoxy Phenyl GSK-3β IC_{50} = 0.22 ± 0.01 μM
86 R = 4-Fluoro Phenyl GSK-3β IC_{50} = 0.20 ± 0.02 μM
87 R = 3-Trifluoromethyl Phenyl GSK-3β IC50 = 0.14 ± 0.01 μM

Fig. 10. Oxadiazole scaffold GSK-3 inhibitors. (All compounds are derived from syntheses carried out by the aforementioned researchers).

moiety forms hydrogen bonds with Pro136 (1.94 Å). Compounds **80**, **81**, **82**, and **83** exhibited the highest activity among all the synthesized compounds, with IC_{50} values of 0.34, 0.39, 0.47, and 0.53 μM. Compared to indomethacin, these compounds (**80**, **81**, **82**, and **83**) were found to inhibit pro-inflammatory mediators, such as TNF-α, IL-1β, and IL-6, *in vitro*, and did not cause any risk of gastric ulcers, indicating the potential of this oxazopyridine scaffold in the development of GSK-3β inhibitors and their applications as anti-inflammatory agents [113]. Compounds **84**, **85**, **86**, and **87** exhibited significant GSK-3β inhibitory effects, with IC_{50} value of 0.13 μM, 0.14 μM, 0.20 μM, and 0.22 μM, respectively. The antidepressant activities of compounds **83**, **84**, **85**, and **86** were evaluated using Forced Swim Test (FST) and Tail Suspension Test (TST) models, and all compounds significantly reduced the immobility time of experimental rats. Compound **84** showed the highest activity and slightly higher efficacy than fluoxetine [114].

4.2.3. *Maleimide-derived GSK-3β inhibitors*

Maleimide derivatives were initially identified through high-throughput screening and were the first reported ATP-competitive selective GSK-3 inhibitors. Compounds **88** and **89** were designed as GSK-3 inhibitors (Fig. 12), with compound **88** exhibiting good inhibitory activity, but also showing CDK inhibitory activity. Although the inhibitory

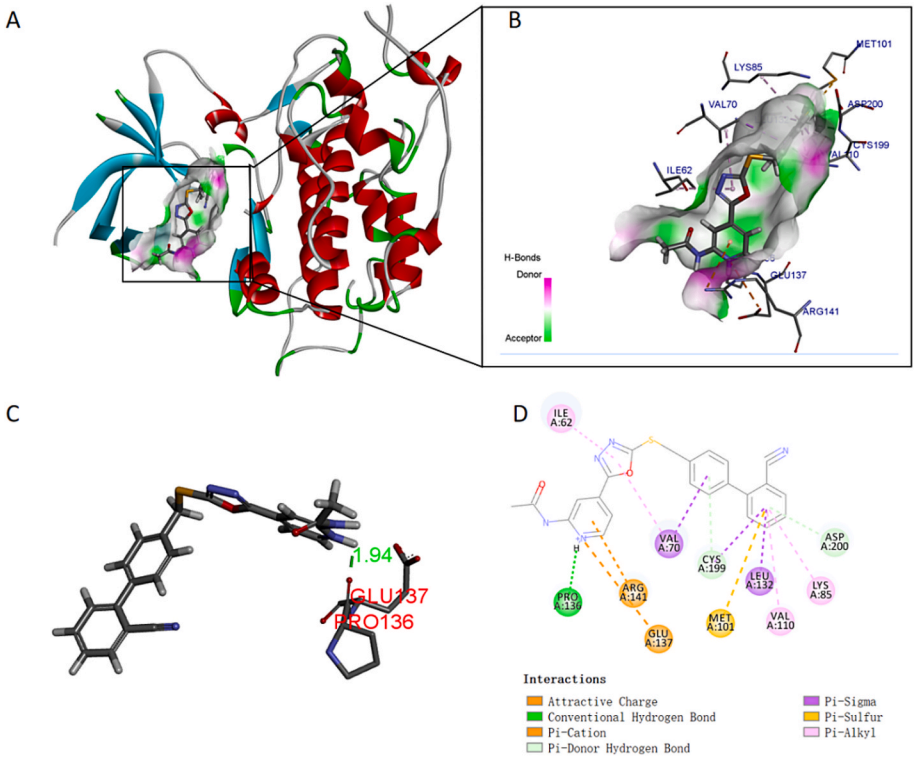


Fig. 11. (A) Docking model of compound **78** and GSK-3 (PDB: 3F88). (B) Docking model of compound **78** and GSK-3 kinase in the active pocket. (C) Compound **78** forms a three-dimensional interaction with Pro136 through hydrogen bonding. (D) 2D docking model of compound **78** and GSK-3.

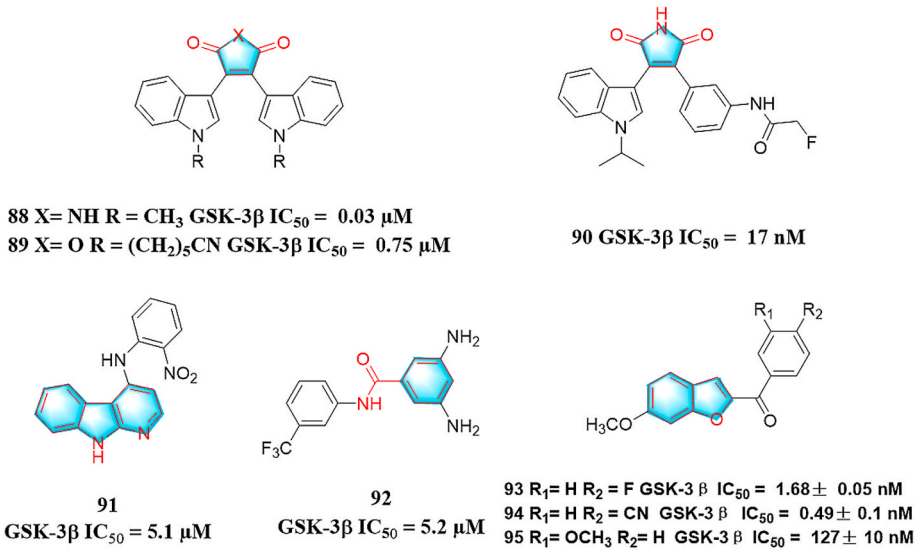


Fig. 12. Maleimide-derived GSK-3β inhibitors (**88**–**90**), Carboline scaffold GSK-3β inhibitors (**91**), Benzamide scaffold GSK-3β inhibitors (**92**), Furan scaffold GSK-3β inhibitors (**93**–**95**). (All compounds are derived from syntheses carried out by the aforementioned researchers).

activity of compound **89** was lower than that of compound **88**, it exhibited good selectivity. Overall, the insertion of dipolymaleimide pharmacophores into the key head groups resulted in good tolerance and inhibition of GSK-3 kinases. It is evident that this new binding platform can impart discrete inhibitory activity to relevant target kinases [115]. Yang et al. reported the discovery of a series of covalent GSK-3β inhibitors by optimizing both non-covalent interactions and reactive groups. Among them, compound **90**, which has a mild α-fluoromethyl amide reactive group, emerged as a selective, covalent inhibitor of GSK-3β, effectively inhibiting the phosphorylation of glycogen synthase and Tau protein and increasing the levels of β-catenin in living cells. In addition, compound **90** is highly permeable and is not a substrate of P-glycoproteins [116].

4.2.4. *Carboline scaffold*

GSK-3 derivatives of carboline are not common, and compound **91** has an inhibitory activity value of 5.1 μM (Fig. 12). Overall, most of the compounds involved have no inhibitory activity against GSK-3 kinases. Therefore, further research on GSK-3 derivatives of carboline is required [117].

4.2.5. Benzamide scaffold

The 3-trifluoromethyl-substituted benzamide compound **92** (Fig. 12) exhibits inhibitory activity against GSK-3 (GSK-3β: 5.2 μM) and almost identical inhibitory activity against FLT-3. Compound **92** also exhibits inhibitory activity against AsPC-1, HCT-116, and U251 cells [118].

4.2.6. Furan scaffold

Compounds **93** and **94** (Fig. 12) have strong inhibitory activity against the GSK-3 kinase of *Plasmodium falciparum* (GSK-3 IC_{50}: 0.49 nM and 1.68 nM), but they also exhibit inhibitory effects against human GSK-3, with selectivity coefficients of 175 and 316, respectively. Although compound **95** has lower inhibitory activity than compounds **93** and **94** against the GSK-3 kinase of *Plasmodium falciparum*, it demonstrates higher selectivity (SI = 559) [119].

4.2.7. Nitrogen-Containing fused heterocycle scaffold

A new class of potent GSK-3 inhibitors, **96**, **97**, and **98** (Fig. 13), has shown significant kinase selectivity in an extensive panel screening. Despite their high clearance rates, these compounds exhibit good activity *in vivo*, reducing phosphorylated Tau levels in three transgenic AD mouse models. Because of their high level of kinase selectivity, radiolabeled versions of these molecules are useful tools for further research [120]. Compound **99** exhibits the highest activity (GSK-3β IC_{50} = 0.56 nM). Compound **99** (50 mg/kg) significantly reduces resting time compared to the known antidepressant drug fluoxetine. The phosphorylation of GSK-3β is mainly mediated by the acute antidepressant-like effect of fluoxetine [121]. The majority of nitrogen-containing fused heterocyclic scaffold compounds discussed in this article exhibit significant nanomolar-level inhibitory activity against GSK-3. Compounds **100** and **101** exhibit significant GSK-3β inhibitory activity, and further evaluation *in vivo* indicated that these compounds are orally bioavailable, brain-permeable GSK-3 inhibitors that can reduce phosphorylated Tau protein levels in a triple-transgenic (3 × Tg) mouse model of AD [122]. We performed molecular docking and simple analysis of the two most active compounds, **100** (Fig. 14) and **101** (Fig. 15), in a nitrogen-containing fused heterocyclic scaffold (PDB: 8FF8). Compounds **100** and **101** were fully embedded in the pocket, with the nitrogen of the pyrimidine and secondary amine acting as hydrogen bond donors and acceptors, respectively, forming hydrogen bonds with the oxygen in the carbonyl group of Val-135 and the hydrogen in the amino group. The nitrogen on the pyridine forms hydrogen bonds with the amino hydrogen of Lys-85. Therefore, compounds **100** and **101** have a strong affinity for GSK-3. However, hydrogen bonds formed between compound **101** and the carbonyl group of Val-135. The shorter distances between compound **101** and Val-135 and Lys-85 in the pocket may explain why compound **101** showed better activity than compound **100**. Compound **102** exhibited inhibitory activity against GSK-3, and its ability to passively diffuse across the blood–brain barrier was evaluated in an *in vitro* model. Kinase activity was confirmed using a cell-based Tau protein hyperphosphorylation model. Therefore, compound **102** was expected to penetrate the central nervous system and exhibit neuroprotective activity against Okadaic acid-induced cell death [123]. Zhang et al. identified that compounds **103** and **104** exhibit potent inhibitory activity against GSK-3β through high-throughput virtual screening followed by experimental validation, with IC_{50} values of 8.48 μM and 2.19 μM, respectively. Molecular dynamics (MD) simulations revealed that Ile62, Val70, Tyr134, and Leu188 in GSK-3β are the critical residues responsible for interactions with compounds **103** and **104** [124]. Andreev et al. demonstrated the indispensable role of the nitrile group in the activity of this series of compounds. A successful rigidization approach afforded compound **105**, which displayed an IC_{50} value of 130 nM against GSK-3β and was further characterized by its metabolic

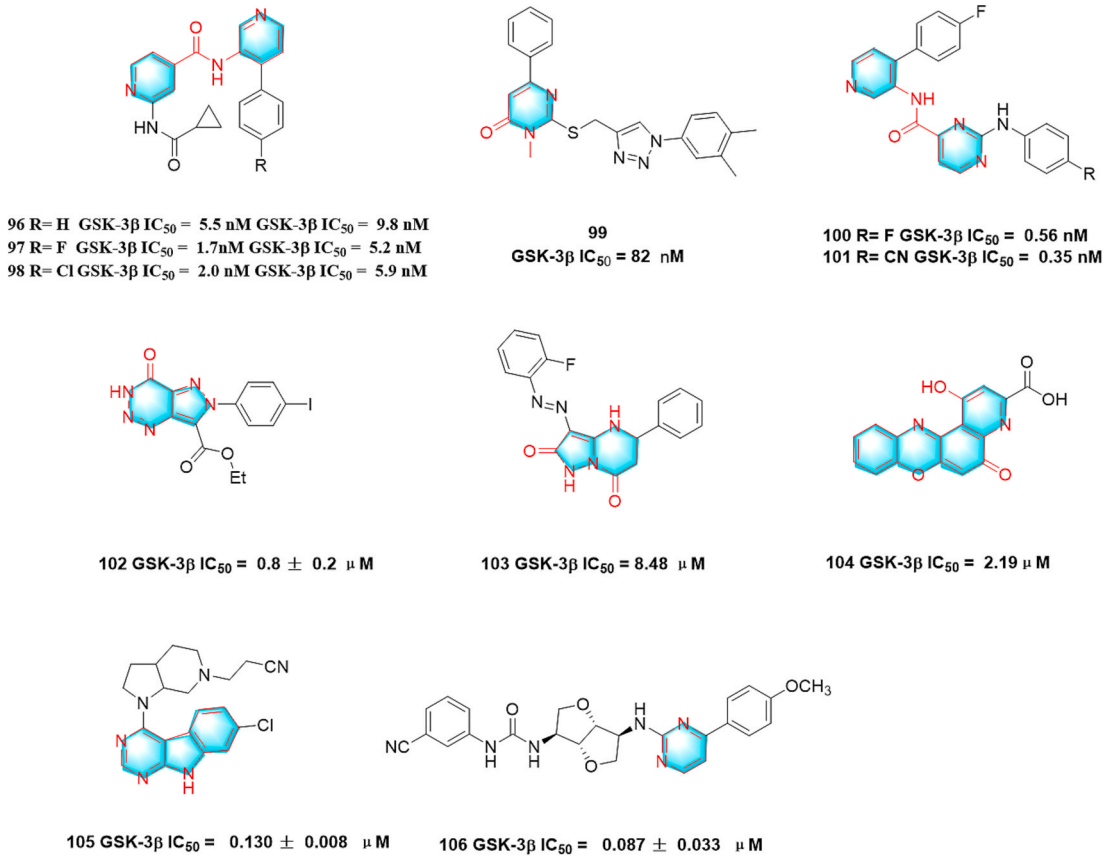


Fig. 13. Nitrogen-containing fused heterocycle scaffold GSK-3β inhibitors. (All compounds are derived from syntheses carried out by the aforementioned researchers).

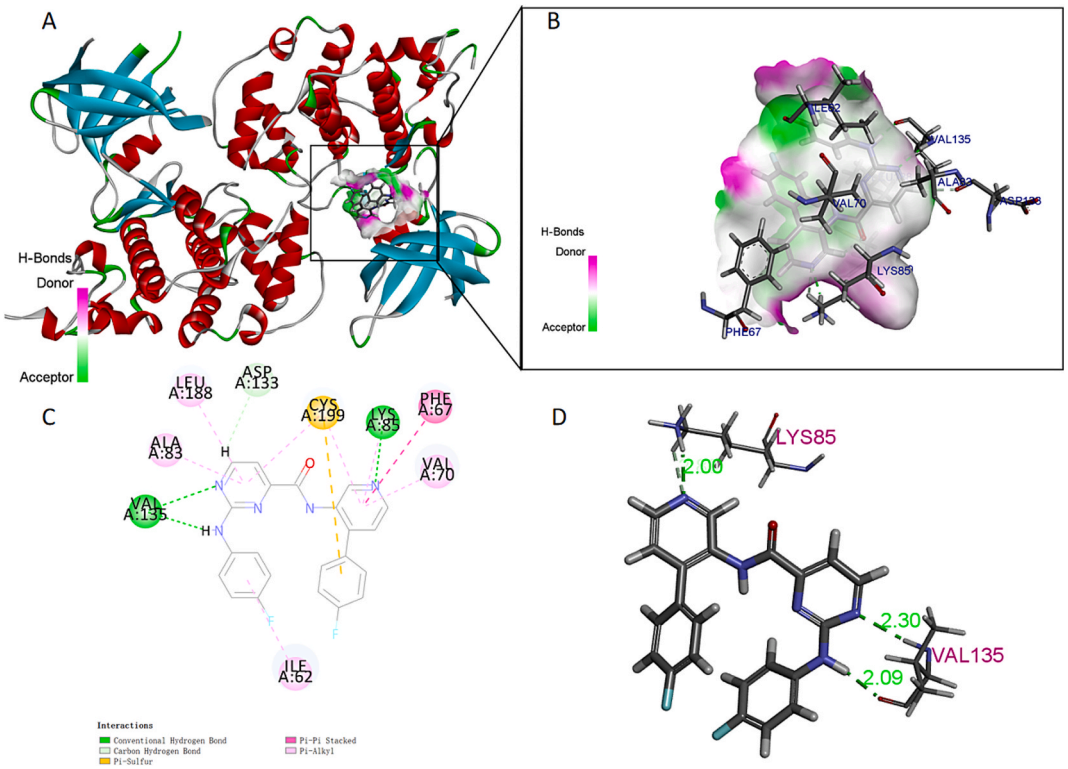


Fig. 14. (A) Docking model of compound **100** and GSK-3 (PDB:8FF8). (B) Docking model of compound **100** and GSK-3 kinase in the active pocket. (C) 2D docking model of compound **100** and GSK-3. (D) Compound **100** forms a three-dimensional interaction with Val135 and Lys85 through hydrogen bonding.

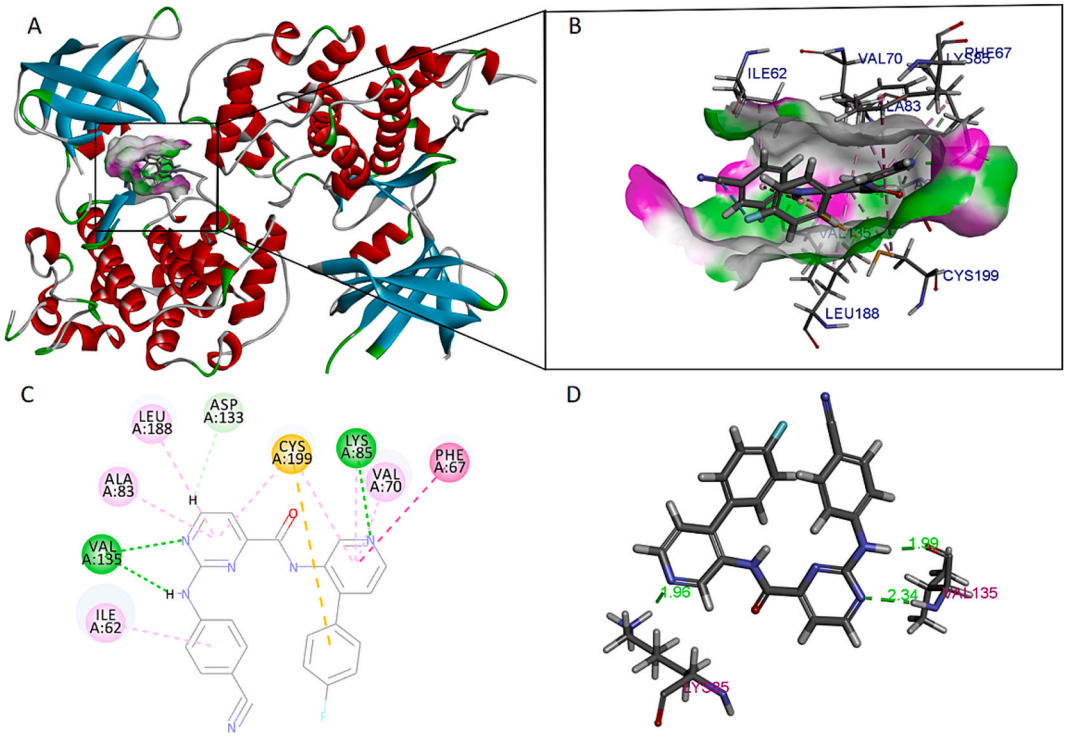


Fig. 15. (A) Docking model of compound **101** and GSK-3 (PDB:8FF8). (B) Docking model of compound **101** and GSK-3 kinase in the active pocket. (C) 2D docking model of compound **101** and GSK-3. (D) Compound **101** forms a three-dimensional interaction with Val135 and Lys85 through hydrogen bonding.

stability. Finally, they determined the putative binding modes of the most potent inhibitors within the ATP binding site of GSK-3β using 1 μs MD simulations [125]. Compound **106** (IC_{50} = 0.087 μM) was more than 100 times more potent than TDZD-8 (IC_{50} = 2 μM), and selectivity for GSK-3β inhibition compared to homologous kinases was observed. *Ex vivo* experiments (using the SH-SY5Y cell line) on Tau hyperphosphorylation revealed promising neuroprotective effects at low-micromolar concentrations [126].

4.2.8. Thiazole scaffold

Compound **107**, which has acryloyl warheads, exhibits significant inhibitory activity against GSK-3 kinase (Fig. 16). Meanwhile, the well-tolerated compound **108** significantly inhibits the release of inflammatory cytokines from SH-SY5Y cells induced by Aβ and can cross the blood–brain barrier before entering the central nervous system to achieve therapeutic effects in an AD model [127]. GSK-3β inhibitors have been identified using structure-based virtual screening. The most active compound, **108** (IC_{50}: 0.71 μM), has also been shown to be active in cell experiments, as predicted by molecular docking and kinetics analysis. Two-dimensional similarity enriches chemical substances [128]. Through synthesis and *in vitro* biological evaluation, compound **109** was found to exhibit inhibitory effects against GSK-3β in the lower-nanomolar range (IC_{50}: 2.1 nM). MD simulation studies of the most effective and selective compounds indicate that the selectivity of these compounds is determined by the Lys85, Thr138, Arg141, and Cys199 residues of GSK-3 [129]. We performed molecular docking and a simple analysis of compound **109** in a thiazole scaffold (PDB: 8FF8; Fig. 17). Compound **109** was completely embedded in the pocket, and the secondary amine formed hydrogen bonds with the Asn64 residue.

4.2.9. Brief Summary

The ATP-binding pocket of GSK-3 is composed of key amino acids, such as Asp 133, Tyr 134, Val 135, and Arg 141, and has high homology with the catalytic regions of other protein kinases. The inhibitors acting on this region are ATP-competitive inhibitors with generally strong activity and can reach nanomolar levels but with poor selectivity. Among them, compound **67**, which had the best GSK-3 inhibitory activity, achieved a low-nanomolar level of activity against GSK-3β, which is highly consistent with the characteristics of ATP inhibitors. Compound **98** is a small molecule with a planar hydrophobic heterocyclic structure. Compound **100** formed two hydrogen bonds with Val 135 of GSK-3. Because of the high level of conservation of ATP-binding sites in all protein kinases, competitive inhibitors have generally poor selectivity and significant toxic side effects. Although various structurally potent small-molecule inhibitors have been developed, progress in clinical research has been slow.

4.3. Non-ATP competitive inhibitor

In 2002, Martinez et al. [130] first reported a class of non-ATP-competitive small-molecule inhibitors that selectively inhibit GSK-3β (Fig. 18), with the parent nucleus being thiadiazolidinone (TDZD). The IC_{50} value of TDZD-8 (**19**) reached 2 μM. Preliminary structure–activity relationship analysis revealed several findings. First, the volume of the substituents on the N2 core of the TDZD structure is crucial for inhibitory activity. Among these substituents, Me was found to be the best. This indicates that this corresponds to the spatial hindrance in GSK-3β. Second, the introduction of aromatic rings, such as benzene, toluene, or naphthalene rings, at N4 enhanced its activity. This indicates that hydrophobic interactions can occur with GSK-3β. Third, when the carbonyl group at position 3 of the parent nucleus changes to a thiocarbonyl group, it maintains its activity, but its solubility decreases. After replacing the oxygen carbonyl group at position 5 with a bioisomeric imine group, the inhibitory activity decreased significantly. This indicates that the 5-carbonyl group plays an important role in binding with GSK-3β.

In 2005, Martinez et al. [131] reported the results of electron isosteric derivatization of the TDZD mother nucleus. Among the five types of heterocyclic compounds, including hydantoines, dithiazolidiniones, thiazoles, maleimides, and triazoles, maleimide compounds generally showed increased activity, whereas the other types of compounds showed lower activity than the TDZD mother nucleus. The structure–activity relationship analysis revealed several findings. First, for maleimide compounds, the inhibitory activity is increased by the substitution of aromatic rings or ester groups on the N atom, while the length of the chain connecting the aromatic ring to the N atom does not affect the activity. When there is an N atom between two carbonyl groups, the activity is the highest, followed by a C. If O is present, the activity decreases significantly, and the two carbonyl groups and the C=C double bond in the parent nucleus are essential for the inhibitory activity. For rhodanines and thiazolidines, the importance of aromatic substituents on N for the inhibitory activity was still demonstrated, but the activity decreased as the length of the chain connecting the aromatic groups to N increased. It is worth noting that, in this type of compound, thiocarbonyl is an essential active group, and replacing it with oxygen carbonyl reduces its activity. Third, analysis of thiazolidinediones, triazolidinediones, and hydrantoins showed that aromatic ring substituents on the N atom between the two carbonyl groups are important for maintaining activity; however, triazolidinediones and hydrantoins have no activity at all. This indicates the importance of S in the TDZD nucleus for its inhibitory activity.

TDZD compounds have two binding sites when interacting with GSK-3β. One is located in the substrate-binding active ring near Arg96, Arg180, and Lys205. There is a well-shaped complementary region. The two benzene rings form an overlapping conformation pointing towards the same side of TDZD. The benzene ring and positively charged Arg92 and Arg96 generate cation π interactions, which partially explain the mechanism of the non-ATP competitive inhibition of TDZD; that is, the inhibitor hinders the normal binding of substrates to the active regions of GSK-3β (Arg96, Arg180, Lys205), thereby inhibiting enzyme-mediated phosphorylation of its substrates. The second binding site is the ATP-binding cavity. Considering that the GSK-3β inhibitory activity of TDZD compounds is closely related to aromatic heterocycles, especially the sulfur atoms in the aromatic heterocycles, it can be inferred that there may be electrostatic interactions between TDZD compounds and the thiol groups of Cys199. This may also explain the high selectivity of TDZD compounds towards GSK-3β [131].

4.3.1. Benzothiazepinone-derived GSK-3β inhibitors

Compounds **110** and **111** show inhibitory activity against GSK-3β in the low-micromolar range and were identified as similar to the reported non-ATP competitive inhibitors (Fig. 19). Furthermore, they have been shown to act in a non-ATP competitive inhibition mode and exhibited

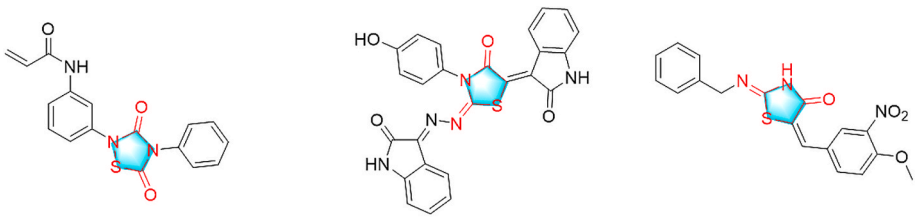


Fig. 16. Thiazole scaffold GSK-3β inhibitors. (All compounds are derived from syntheses carried out by the aforementioned researchers).

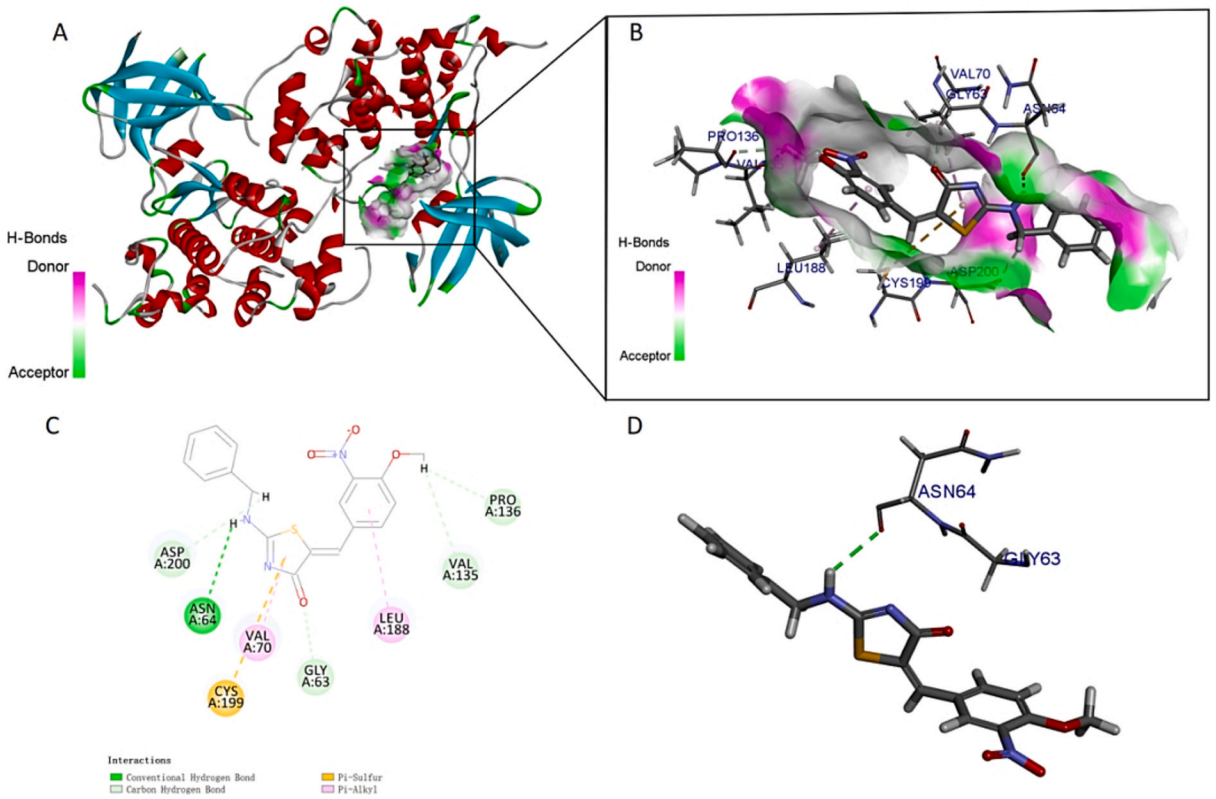


Fig. 17. (A) Docking model of compound **109** and GSK-3 (PDB:8FF8). (B) Docking model of compound **109** and GSK-3 kinase in the active pocket. (C) 2D docking model of compound **109** and GSK-3. (D) Compound **109** forms a three-dimensional interaction with Val135 and Lys85 through hydrogen bonding.

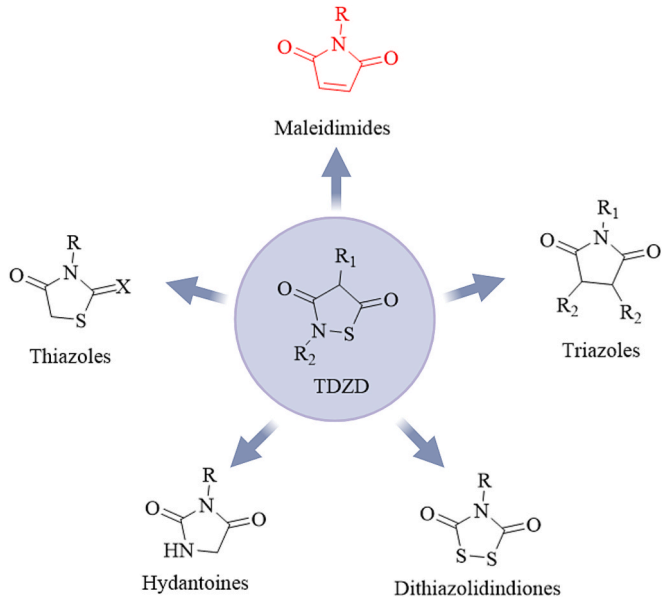


Fig. 18. Modification of TDZD.

good specificity in a panel test of 16 other protein kinases [132]. The IC_{50} values of compounds **112**, **113**, and **114** are 25.0 μM, 27.8 μM, and 23.0 μM. Through kinetic analysis, it has been proven that compound **114** has a reversible non-ATP competitive mechanism for inhibiting GSK-3β. In addition, it did not show any inhibitory activity against the other 13 protein kinases, indicating, to some extent, that benzothiazepinone compounds have good specificity for GSK-3β [133].

4.3.2. *GSK-3β inhibitors with anthracenone-isoxazole scaffold*

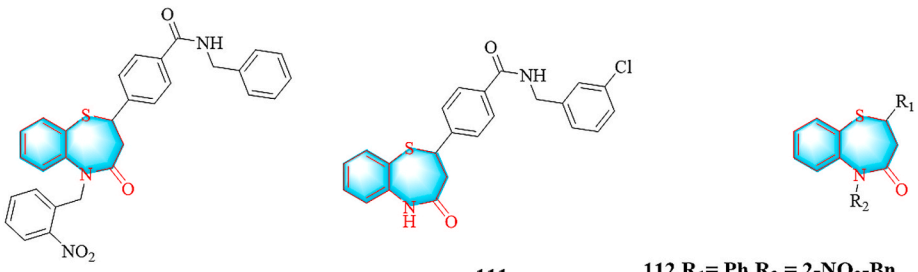
Compounds **115** and **116** (Fig. 20) showed IC_{50} values of 1–4 μM. In addition, **115** and **116** extended their interactions with Phe67, Lys85, or Ser66 through their COOH or OH moieties, respectively. These residues play a role in GSK-3-substrate binding. Thus, the improvement in their ability to inhibit GSK-3 is due to the additional interactions mediated by **115** and **116** [134].

4.3.3. *Other GSK-3β inhibitors*

Enzymatic assays and kinetic studies have shown that compound **117** is a competitive inhibitor of GSK-3β (Fig. 20), with significant kinase selectivity and subtype selectivity. Its efficacy increased by more than 310-fold compared with the lead compound Isoorientin. Structure-activity relationship analysis and the mechanism of action determined using the in silico model indicate that hydrophobic, π-cation, and multipolar interactions between orthogonal and substrate positions are key factors for GSK-3β inhibition and selectivity. These research findings provide new insights into the discovery of drugs targeting GSK-3β [135].

4.3.4. *Brief Summary*

Theoretically, competitive inhibitors that act on the non-ATP binding region of GSK-3 have better selectivity and fewer side effects, making them more likely to be used as effective drugs. Although research on non-ATP competitive GSK-3β inhibitors started relatively late and there are not many structural types, TDZD-8 has shown good enzyme selectivity. The clinical study of tideglusib (**6**), a non-ATP competitive GSK-3β inhibitor, was terminated, which undoubtedly makes research on non-ATP inhibitors more challenging. Therefore, research on non-ATP inhibitors faces more difficult tasks, and expanding the structural diversity of non-ATP competitive GSK-3β inhibitors remains a top priority.

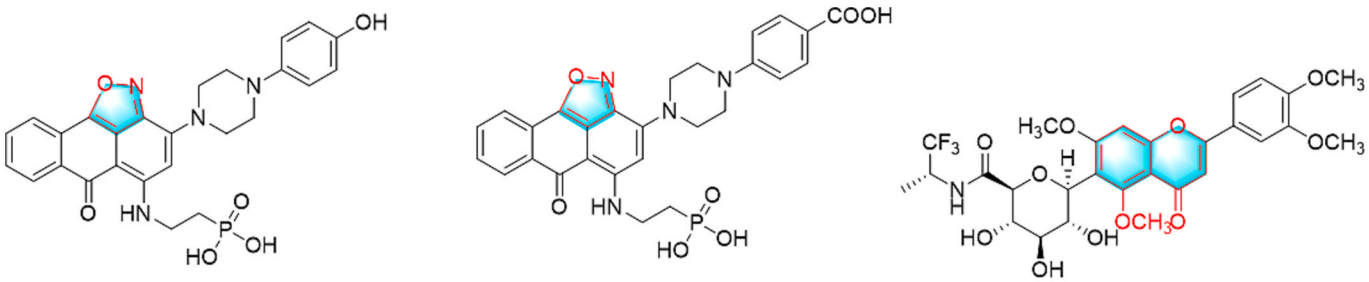


110
GSK-3β IC_{50} = 28 μM

111
GSK-3β IC_{50} = 25 μM

112 R_1= Ph R_2 = 2-NO_2-Bn
GSK-3β IC_{50} = 25 μM
113 R_1= Ph R_2 = 2-COOMe-Bn GSK-3b IC_{50} = 27.8 μM
114 R_1= $PhCH_2$ R_2= 2-NO_2-Bn G_5K-3b IC_{50} = 23 μM

Fig. 19. Benzothiazepinon-ederived GSK-3β inhibitors. (All compounds are derived from syntheses carried out by the aforementioned researchers).



115
GSK-3β IC_{50} = 1-4 μM

116
GSK-3β IC_{50} = 1-4 μM

117
GSK-3β IC_{50} = 0.6μM

Fig. 20. GSK-3β inhibitors with anthracenone-isoxazole scaffold (**115**, **116**), GSK-3β inhibitors (**117**). (All compounds are derived from syntheses carried out by the aforementioned researchers).

4.4. Allosteric inhibitors of GSK-3β inhibitor

Allosteric regulation involves the regulation of enzyme activity by altering the conformation of the enzyme through specifically binding to regions outside the active sites of inhibitors and enzyme molecules.

4.4.1. Quinoline-3-carbohydrazide scaffold-based GSK-3β inhibitors

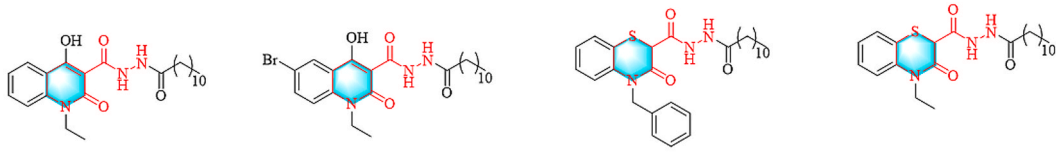
Compounds **118** (IC_{50} = 2.01 ± 0.18 μM) and **119** (IC_{50} = 2.48 ± 0.26 μM), non-competitive inhibitors of ATP binding, exhibited good GSK-3 inhibition and acted as non-competitive inhibitors of ATP binding, as an increase in the ATP concentration from 1 μM to 50 μM did not interfere with enzyme inhibition. Compound **116** improved delayed myogenesis in congenital myotonic dystrophy type 1 (CDM1) myoblasts, whereas compounds **116** and **117** exhibited neuroprotective effects in SMA-derived cells (Fig. 21). These findings suggest that allosteric modulators of GSK-3β could potentially be used for the treatment of DM1, SMA, and other chronic diseases, with GSK-3β inhibition having therapeutic effects [136].

4.4.2. Benzothiazepinone-derived GSK-3β inhibitors

Compound **120** (IC_{50} = 8 μM) and compound **121** (IC_{50} = 10 μM) are novel conformational modulators and substrate-competitive inhibitors of GSK-3β (Fig. 21). Different modes of action were demonstrated through dynamic experiments. In addition, the kinase profile of compound **121** was determined, and it showed little or no activity towards 10 protein kinases at 100 μM, indicating good selectivity [137].

5. Study on the medicinal properties of GSK-3 inhibitors

At present, the development of GSK-3 inhibitors faces several key challenges and problems. First, an ideal GSK-3 inhibitor should selectively modulate GSK-3 activity in diseased cells without affecting GSK-3 or other kinases in normal cells. However, due to the high conservation of ATP-binding sites across all protein kinases, most competitive



118
GSK-3β IC_{50} = 2.8 ± 0.4 μM

119
GSK-3β IC_{50} = 2.01 ± 0.18 μM

120
GSK-3β IC_{50} = 8 μM

121
GSK-3β IC_{50} = 10 μM

Fig. 21. Quinoline-3-carbohydrazide scaffold-based GSK-3β inhibitors (**118**, **119**), Benzothiazepinonederived GSK-3β inhibitors (**120**, **121**). (All compounds are derived from syntheses carried out by the aforementioned researchers).

inhibitors exhibit poor selectivity, leading to significant toxicity associated with existing GSK-3 inhibitors. Several GSK-3 inhibitors have been discontinued in clinical trials due to severe side effects, including pneumonia, nausea, vomiting, breathing difficulties, pulmonary toxicity, and angina. Moreover, the pharmacokinetic properties of GSK-3 inhibitors require further optimization. Additionally, drug resistance remains a critical challenge for current GSK-3 inhibitors. To address these issues, various strategies have been successfully employed, such as dual-target drug design and Proteolysis Targeted Chimeras (PROTACs).

5.1. Dual target inhibitors

The design of a multi-target inhibitor could potentially be achieved by fusing two or more drugs or pharmacophores with different targets in the same molecule. Such inhibitors can inhibit different cellular pathways or compensatory mechanisms, and have a wide range of biological activities. They can overcome drug resistance caused by long-term use of single-target drugs and avoid drug-drug interactions. Therefore, the development of multitarget drugs is considered an effective way to discover new drugs and has great development prospects.

The design of a multi-target inhibitor can be achieved by fusing two or more drugs or pharmacophores with different targets in the same molecule. Such inhibitors can inhibit different cellular pathways or compensatory mechanisms, and have a wide range of biological activities. They can overcome drug resistance caused by long-term use of single-target drugs and avoid drug-drug interactions. Therefore, the development of multitarget drugs is considered an effective way to discover new drugs and has great development prospects. Maleimide DPCI hybrid, as a dual inhibitor targeting glutaminyl cyclase (QC) and GSK-3β. Compound 122 (Fig. 22) alleviates cognitive deficits and reduces anxiety-like behavior in 3 × Tg AD mice. In addition, treatment with compound **122** reduced the accumulation of Aβ and pyroglutamate-Aβ in the brains of 3 × Tg AD mice, the generation of hyperphosphorylated Tau protein, and the activity of QC and GSK-3β [138].

Compound **123** (Fig. 23) is a leading molecule that prioritizes the inhibition of acetylcholinesterase (AChE)/GSK-3β (AChE IC_{50} = 1.2 ± 0.1 nM; GSK-3β IC_{50} = 22.2 ± 1.4 nM). In addition, compound **123** exhibits high activity towards GSK-3, with inhibition rates of 83.69 % and 67.94 % against DYRK1α and DYRK1β, respectively, at 20 μM. Compound **123** also exhibits good blood–brain barrier permeability and inhibits Tau phosphorylation. In a Morris water maze model, oral administration of compound **123** resulted in significant cognitive improvement in mice with polyamine-induced cognitive impairment [139]. Similarly, another study used dual-target inhibitors of GSK-3 and AChE, combining different GSK-3 inhibitors with tacrine. Compound **124** exhibits a significant inhibitory activity against AChE and GSK-3, with good efficacy and balance (AChE: IC_{50} = 51.1 nM; GSK-3β IC_{50} = 89.3 nM), significantly improving cognitive deficits in polyamine-induced amnesia in mice, and effectively reducing Tau protein phosphorylation at Ser199 and Ser396 sites in differentiated SH-SY5Y cells stimulated with glyceraldehyde (GA). In addition, compound **124** exhibits suitable pharmacokinetic properties, good kinase selectivity, and moderate neuroprotection against GA-induced decreases in SH-SY5Y cell viability and neuronal damage [140].

Compound **125** (Fig. 23) serves as an inhibitor of AChE (IC_{50} = 6.5 nM) and hGSK-3β kinase activity (IC_{50} = 66 nM). At 20 μM, it also exhibits a good inhibitory effect on the self-aggregation of β-amyloid protein (inhibition rate = 46 %). Western blotting analysis showed that compound **125** inhibits the excessive phosphorylation of Tau protein in N2a Tau cells in mouse neuroblastoma. *In vivo* studies have confirmed that compound **125** significantly improves cognitive impairment in ICR mice treated with scopolamine, and its liver toxicity is lower than that of tacrine [141].

Compound **126** (Fig. 24) has strong inhibitory effects against GSK-3β (IC_{50} = 71 nM) and DYRK1A (IC_{50} = 103 nM), respectively. Molecular models and kinetic studies have confirmed that compound **126** can interact with the ATP-binding pockets of GSK-3β and DYRK1A. Immunoblotting analysis showed that compound **126** inhibits okadaic-acid-induced excessive phosphorylation of the Tau protein in SH-SY5Y cells. In addition, compound **126** exhibited good blood–brain barrier penetration. More importantly, compound **126** improves learning and memory impairment in APP/PS1/Tau transgenic mice [65]. Subsequently, further structural modifications were made based on compound **126**, while retaining the basic skeleton. The ester was replaced with methoxy and cyclopropanecarboxylic acid was replaced with 3-fluorophenylacetic acid, resulting in compound **127** with an activity similar to that of the lead compound [142].

Compound **128** (Fig. 24) exhibits dual-inhibitory activity against CDK2/GSK-3β, with an IC_{50} value of 37.77 nM against CDK2 and 32.09 nM against GSK-3β. The most effective compound, Compound **128**, causes cell cycle arrest in the G2/M phase of MCF-7 cells, thereby inducing apoptosis [143].

Compound **129** exhibits good inhibitory activity against both GSK-3 and BACE kinases [144]. *In silico* data drove the synthesis of appropriately modified benzoxazinone and indole, and biochemical analysis showed their behavior as allosteric inhibitors of hGSK-3β. The most active compounds, **130**, **131**, and **132** (Fig. 25), were evaluated for their potential antioxidant properties in human neuroblastoma cell lines (IMR 32, undifferentiated, and neuronally differentiated cells) by assessing their protective effects against H_2O_2 cytotoxicity and reactive oxygen species (ROS) production. The results showed that, even at lower doses, the test compound had strong efficacy in combating H_2O_2-induced oxidative stress (50 μM H_2O_2) and preventing ROS formation. In addition, within the analyzed concentration range (0.1 to 50 μM), the tested compound did not show any cytotoxic effects, as assessed using an LDH-release assay [145].

Compounds **133** (IC_{50} in K562 = 17.1 ± 1.9 μM) and **136** (IC_{50} in K562 = 7.8 ± 7.9 μM), **134** (IC_{50} in HeLa = 11.2 ± 7.9 μM), and **135** (IC_{50} in A549 = 22.6 ± 22.3 μ M) all exhibited good inhibitory effects (Fig. 26). Compound **136** exhibits highly selective antiproliferative activity against K562 cells (IC_{50} = 7.8 μM) and induces K562 cell apoptosis in a dose-dependent manner. By reducing the expression levels of cyclin A and CDK2, which play crucial roles in DNA replication and passage through the G2 phase, the cell cycle of K562 cells is arrested in S phase. In addition, compound **136** downregulates the expression of p-GSK-3β (Ser9), β-catenin, and c-myc protein, upregulates the expression of GSK-3β, and provides clues for the development of dual CDK2/GSK-3β (Ser9) phosphorylation inhibitors for cancer chemotherapy [146].

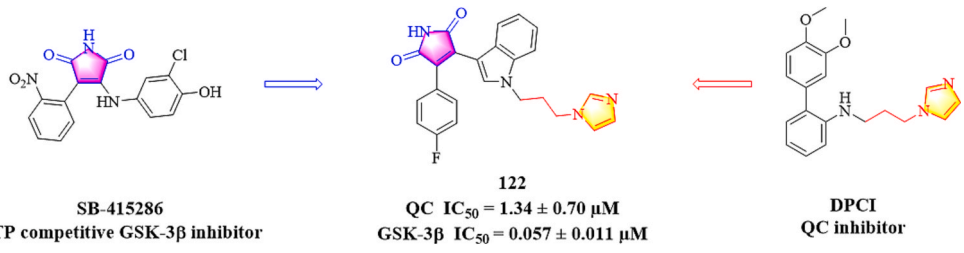


Fig. 22. QC/GSK-3β dual targets inhibitor. (All compounds are derived from syntheses carried out by the aforementioned researchers).

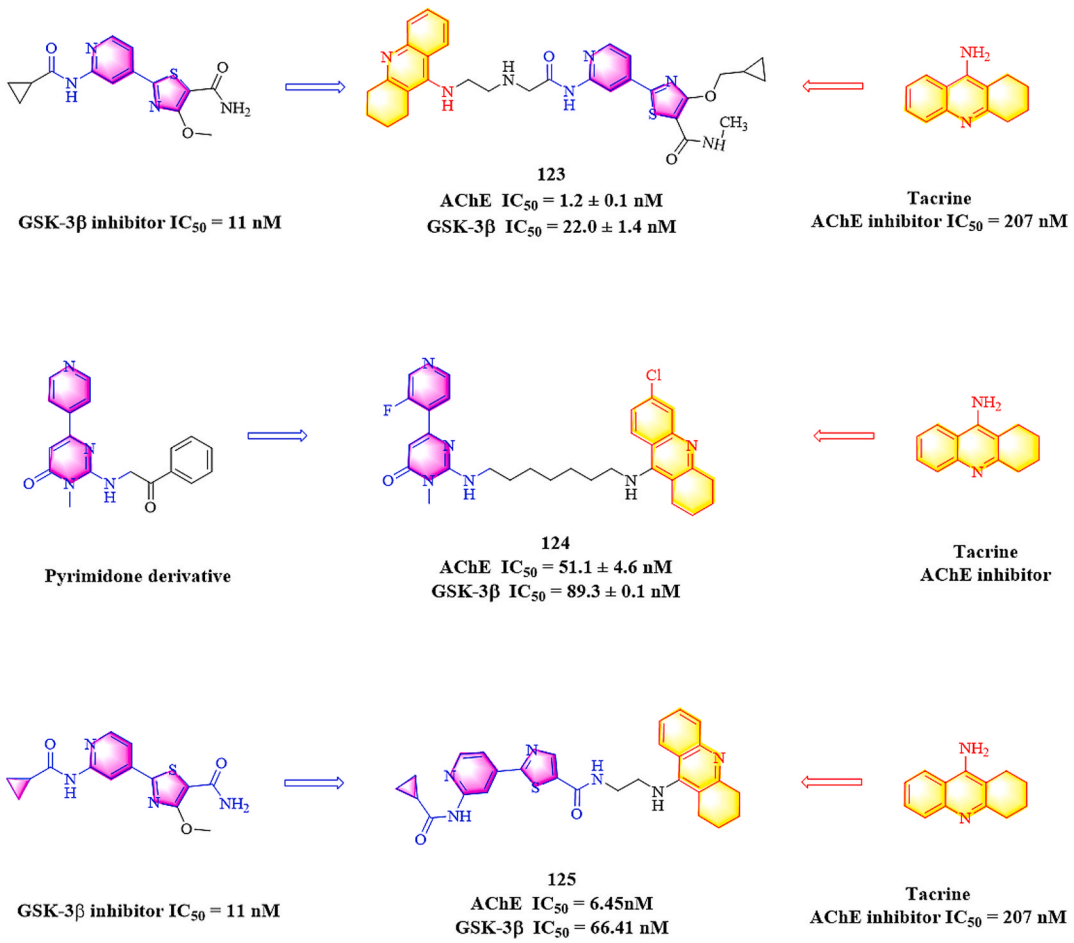


Fig. 23. AchE/GSK-3β dual targets inhibitor. (All compounds are derived from syntheses carried out by the aforementioned researchers).

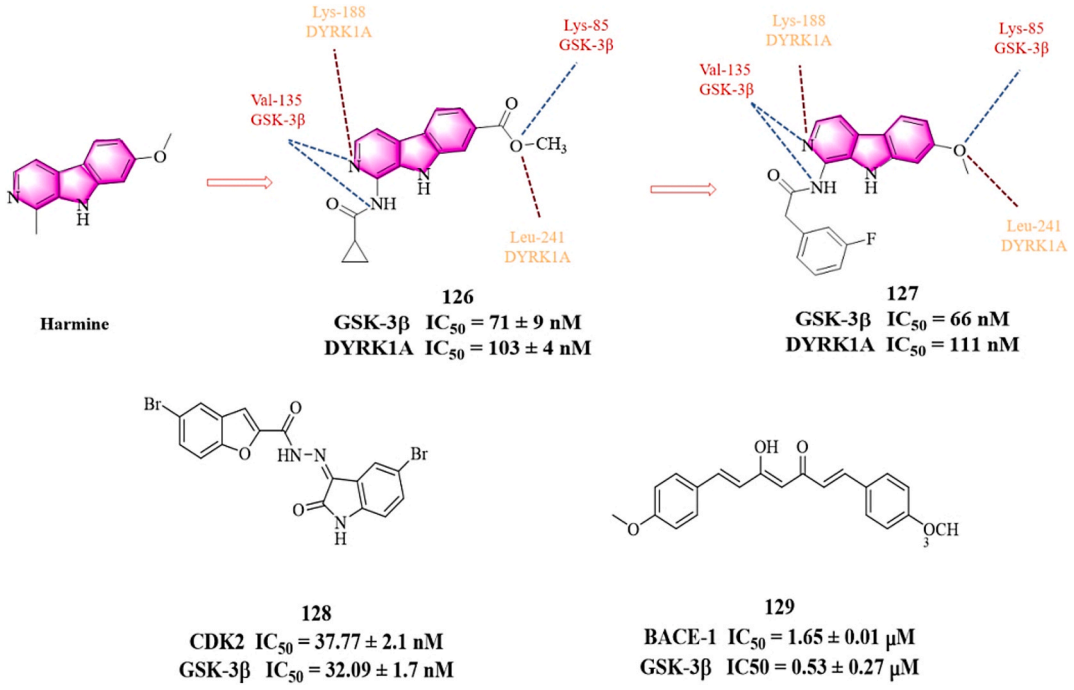


Fig. 24. DYRK1A/GSK-3β dual targets inhibitor (**126, 127**), CDK2/GSK-3β dual targets inhibitor (**128**), BACE-1/GSK-3β dual targets inhibitor (**129**). (All compounds are derived from syntheses carried out by the aforementioned researchers).

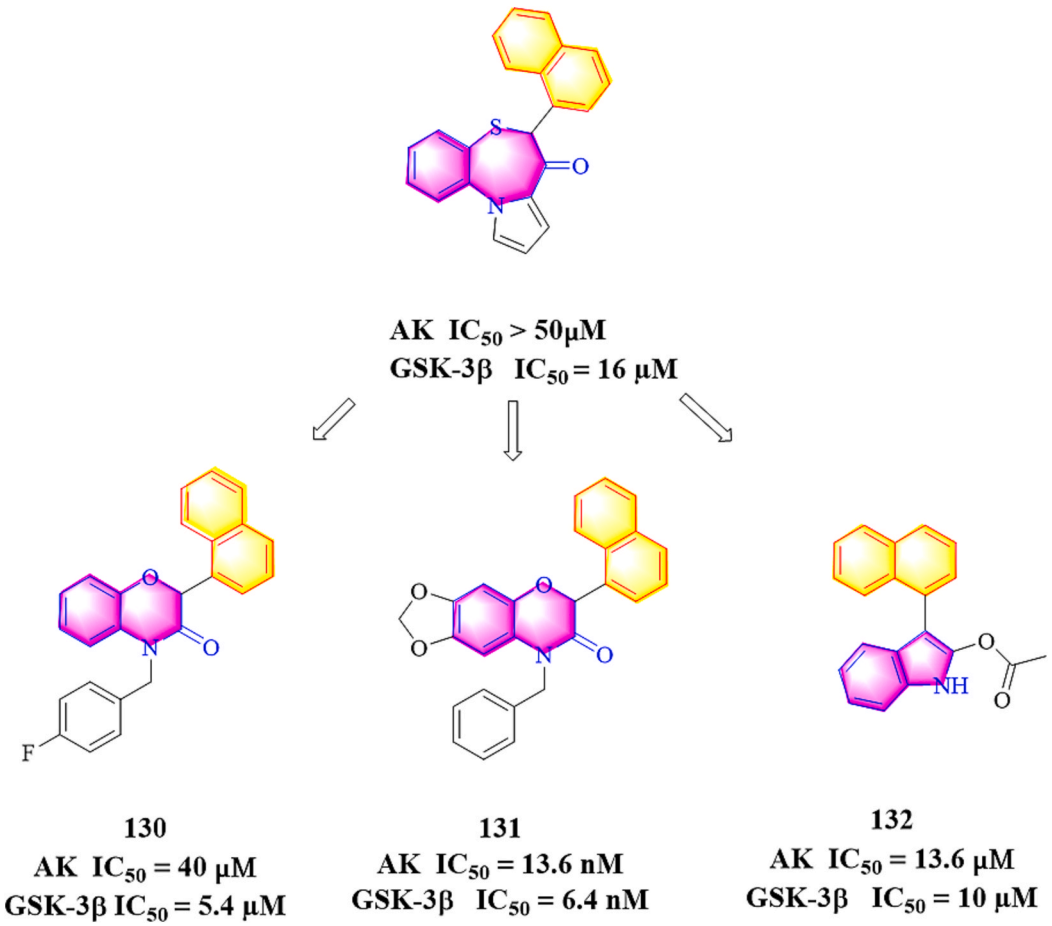


Fig. 25. AK/GSK-3β dual targets inhibitor. (All compounds are derived from syntheses carried out by the aforementioned researchers).

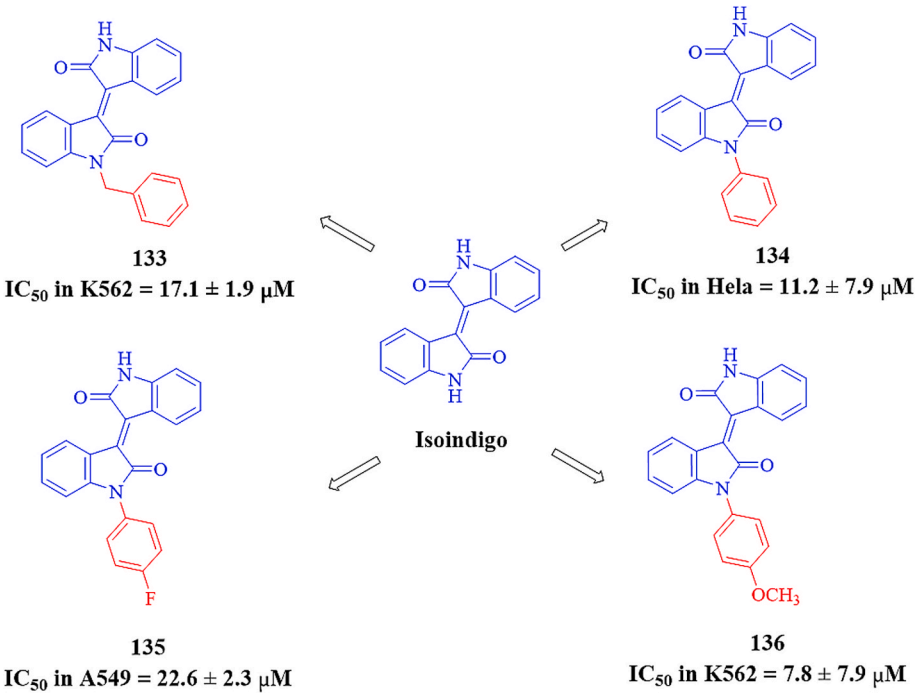
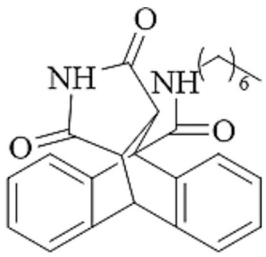


Fig. 26. CDK2/GSK-3β dual targets inhibitor. (All compounds are derived from syntheses carried out by the aforementioned researchers).



137

GSK-3β IC_{50} = 9 μM

Fig. 27. Calcium channel regulators/GSK-3β dual targets inhibitor.

Bisi et al. reported a non-toxic lead compound **137** (synthesized to obtain, IC_{50} = 9 μM) based on polycyclic maleimide (Fig. 27), which had calcium-modulating and brain-targeted properties and could simultaneously regulate both neuronal calcium channels and GSK-3β [147].

Compound **138** (Fig. 28) exhibited combined inhibitory activity against GSK-3β (IC_{50} = 0.17 μM) and CK-1δ (IC_{50} = 0.68 μM). In particular, classic ATP competition against CK-1δ, as well as the eutectic of compound **138** within GSK-3β confirmed the covalent interaction between cyanoacrylamide warheads and Cys199, which may contribute to the development of more effective covalent inhibitors against GSK-3β. Preliminary studies using an *in vitro* model of Parkinson's Disease showed that compound **138** has no cytotoxicity and exhibits neuroprotective activity. These results encourage further research to validate GSK-3β/CK-1δ inhibition as a possible new strategy for treating neuroinflammation and degenerative diseases [148].

Based on the reported connection between histone deacetylases (HDACs) and GSK-3β, the discovery and biochemical characterization were reported for the first-in-class hit compound that is able to exert promising anti-AD effects by modulating proteins in the low-micromolar concentration range. Compound **139** (Fig. 29) induced an increase in histone acetylation and a reduction in Tau phosphorylation. It was non-toxic and protective against H_2O_2 and 6-OHDA stimuli in SH-SY5Y and CGN cell lines, respectively [149].

6. PROTACs

PROTACs utilize the intracellular ubiquitin–proteasome system to selectively degrade specific target proteins through catalysis, representing an innovative model in the field of drug discovery [150]. PROTAC is a small molecule compound composed of three parts, including a target protein binding ligand, an E3 ubiquitin ligase ligand, and a linker connecting these two ligands. PROTAC specifically binds to the target protein through its target protein binding ligand, while recruiting E3 ubiquitin ligase through its E3 ubiquitin ligase ligand to ubiquitinate the target protein. Proteins modified with ubiquitination are recognized and degraded by intracellular proteasomes, thereby achieving specific degradation of the target protein, rather than simply inhibiting protein activity like traditional drugs. This technology provides a new strategy for treating various diseases, especially in targeting proteins that are difficult for traditional drugs to target, such as non-enzyme active proteins and protein–protein interaction interfaces, demonstrating significant advantages (Fig. 30).

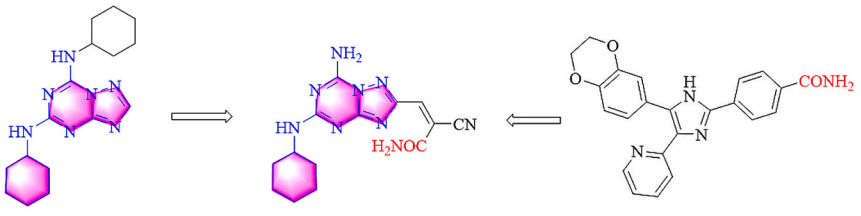
Jiang et al. [73] designed and synthesized a series of small-molecule protein degraders (PROTACs) targeting heterodimeric chimeras based on the E3 ubiquitin ligase cereblon. Most PROTACs exhibit good inhibitory activity, with IC_{50} values at double-digit nanomolar levels and moderate protein-degradation ability towards GSK-3β. Compound PG-21 (**18**) effectively degrades GSK-3β in a dose-dependent manner, inducing 44.2 % protein degradation at a concentration of 2.8 μM. (Fig. 29).

7. Conclusion

GSK-3β has two important active binding sites. The first is the ATP-binding site. Due to the high conservation of this site among all protein kinases, most inhibitors acting at this site have poor selectivity and may cause more adverse reactions, greatly limiting their potential for final drug development. The vast majority of existing GSK-3β inhibitors are ATP-competitive, with only a few showing good selectivity. The second site is a substrate-specific and highly conserved non-ATP binding site. This site is a positively charged pocket composed of Arg96, Arg180, Lys205 and Tyr216. Inhibitors that act at this binding site are expected to exhibit high selectivity [151,152].

An increasing number of natural products have been found to have inhibitory potential against GSK-3 and have entered clinical practice and research in the past decade, which broadens the path and foundation for subsequent research. Research and development of small-molecule inhibitors of GSK-3 are gradually increasing and the inhibitory activity demonstrated in this research has increased to the nanomolar level. Some of the inhibitors have high affinity for GSK-3, while others exhibit good pharmacokinetics *in vivo*. However, these compounds are not perfect, as most inhibitors are ATP-competitive inhibitors that competitively bind to ATP-binding sites, leading to adverse off-target effects and potential effects on other highly conserved protein kinases with an ATP-binding domain. Given the current issues, the development of new GSK-3β inhibitors and non-ATP competitive inhibitors may become a new research direction, with the potential to develop effective drugs with reduced adverse reactions. Allosteric inhibitors target hydrophobic regions far from ATP binding sites, regulate kinase activity by inducing conformational changes in ATP binding pockets, prevent the interaction between GSK-3β and ATP to achieve highly selective inhibition of GSK-3β.

To address the off-target side effects of GSK-3 inhibitors, two



138

CK-1δ IC_{50} = 5.0 ± 0.3 μM
GSK-3β IC_{50} > 40 μM

CK-1δ IC_{50} = 13.6 μM
GSK-3β IC_{50} = 10 μM

CK-1δ IC_{50} = 0.3 μM

Fig. 28. CK-1δ/GSK-3β dual targets inhibitor. (All compounds are derived from syntheses carried out by the aforementioned researchers).

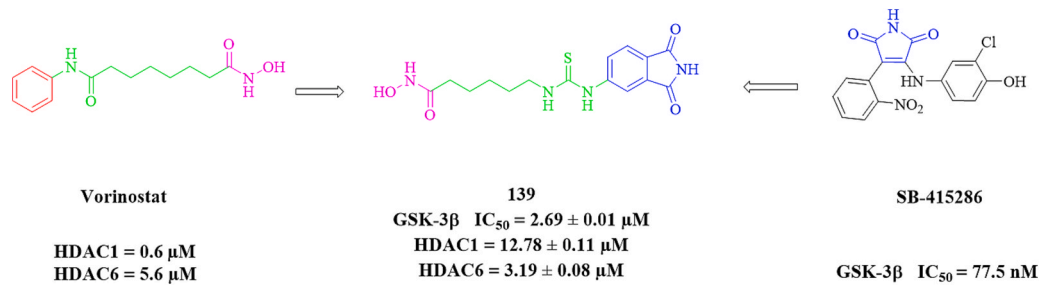


Fig. 29. HDAC/GSK-3β dual targets inhibitor. (All compounds are derived from syntheses carried out by the aforementioned researchers).

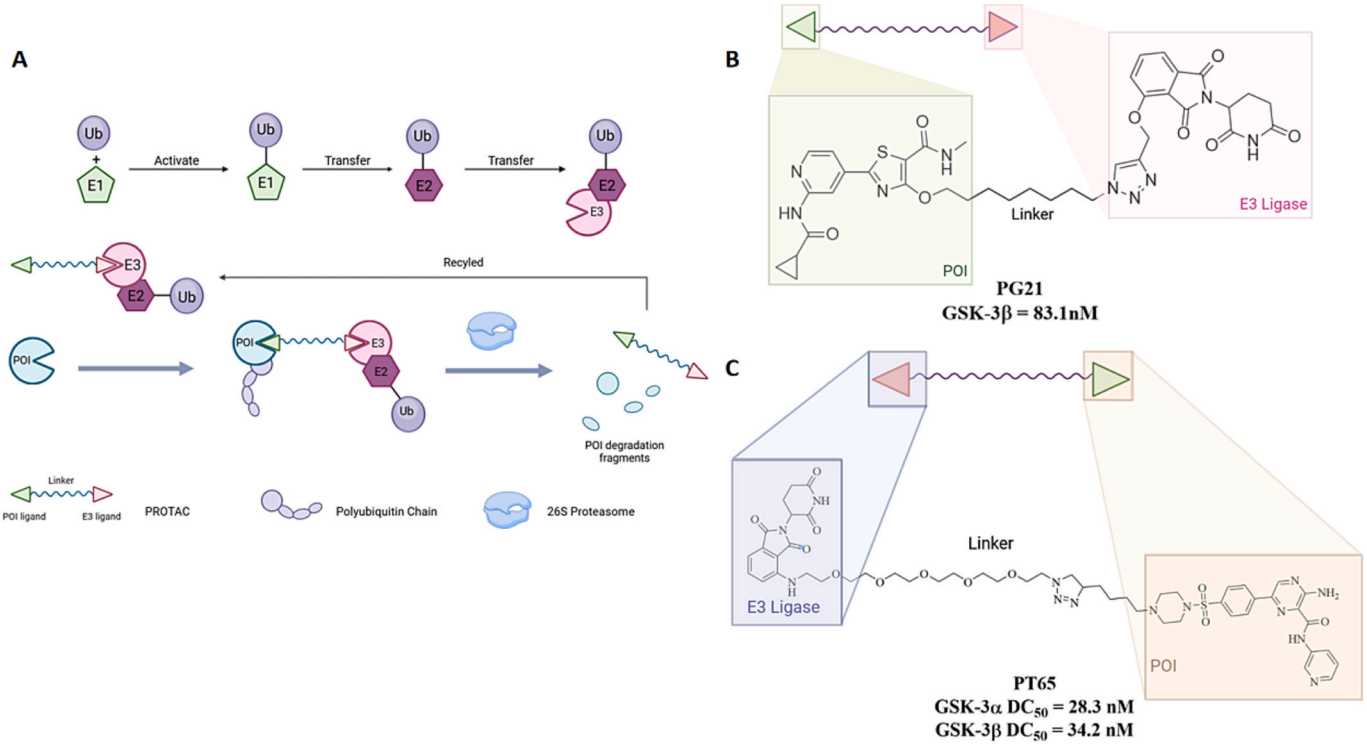


Fig. 30. (A) The strategy of GSK-3β degradation. The mechanism of PROTACs based on the UPS. UPS consists of specific enzymes (E1, E2 and E3) modifying proteins with ubiquitin and the proteasome degrading the ubiquitin-tagging proteins. PROTAC contains a POI ligand, an E3 ligand and a linker. The E3-PROTAC-POI ternary complex induces the polyubiquitination and proteasome-mediated degradation of POIs. (B) Chemical structures of the reported GSK-3β PROTAC (PG21). (C) Chemical structures of the reported GSK-3β PROTAC (PT65).

compounds, PG-21 (**18**) and PT-65 (**17**), have been used in clinical trials to convert GSK-3 inhibitors into PROTAC drugs. In addition, converting drugs into dual-target inhibitors is a hot topic in the field of drug development. For example, research on dual targets such as GABA transaminase and GSK-3, CDK9 and GSK-3, DYRK1A and GSK-3β, GSK-3 and PDE7 and GSK-3 and AchE is increasing. GSK-3 inhibitors can be used to treat a wide range of diseases, as GSK-3 plays indispensable roles in neurodegenerative diseases, diabetes, cancer and inflammation. Among these disorders, GSK-3 inhibitors are more commonly used in research on neurodegenerative diseases, particularly AD. Most dual-target inhibitors of GSK-3 that have entered clinical practice are focused on AD. They all demonstrate strong neuroprotective and anti-AD effects. Patients with AD typically require long-term treatments. Currently, the medical community primarily uses medications and psychological therapy to control disease progression and delay symptom deterioration. However, there is currently no complete cure for AD; therefore, the research path for AD is difficult and time-consuming. Research on GSK-3 inhibitors may provide new insights into AD treatment.

CRediT authorship contribution statement

Ya-lan Wang: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Ke Sun:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jinying Liu:** Writing – review & editing, Supervision. **Yin-sheng Quan:** Investigation, Data curation. **Feng-zhi Lu:** Investigation, Data curation. **Zhe-shan Quan:** Investigation, Data curation. **Xiao-ting Li:** Investigation, Data curation. **Qing-kun Shen:** Supervision, Funding acquisition. **Tian Luan:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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