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Unlocking the therapeutic potential of protein kinase inhibitors in neurodegenerative and psychiatric disorders

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Abstract

Protein phosphorylation is a fundamental regulatory mechanism governing a broad spectrum of cellular processes. In the nervous system, it is critical for modulating neurotransmitter release, synaptic plasticity, neuronal excitability, and cell survival. Dysregulation of protein kinase activity is closely linked to the pathogenesis of various neurological and psychiatric disorders, positioning several kinases as promising therapeutic targets. Although protein kinase inhibitors (PKIs), a major class of compounds that modulate kinase activity, have shown considerable therapeutic success in oncology, their application in neurological diseases remains in the early stages of exploration. Of the 82 PKIs approved by the Food and Drug Administration (FDA), 37 are now in various preclinical and clinical trials for neurological conditions, primarily targeting signaling pathways mediated by key protein kinases implicated in these diseases. This review examines the roles of critical protein kinases and the therapeutic effects of their inhibitors in neurodegenerative, psychiatric, and selected neurological disorders, such as autism spectrum disorders (ASD) and epilepsy. We focus on Abelson kinase I (ABL1), calmodulin-dependent kinase II (CaMKII), casein kinase 1δ (CK1δ), c-Jun N-terminal kinase (JNK), cyclin-dependent kinase 5 (CDK5), dual-specificity tyrosine-phosphorylated and regulated kinase 1A (DYRK1A), leucine-rich repeat kinase 2 (LRRK2), extracellular signal-regulated kinase 1/2 (ERK1/2), glycogen synthase kinase 3β (GSK3β), mammalian target of rapamycin (mTOR), p38 mitogen-activated protein kinase, and protein kinase C (PKC) in neurodegenerative diseases. Additionally, we discuss CaMKII, CDK5, ERK1/2, PI3K/AKT/GSK3, protein kinase A (PKA), and PKC in psychiatric disorders, focusing on schizophrenia and mood disorders, and analyze GSK3β, ERK1/2, and mTOR in ASD and epilepsy. This review underscores the therapeutic potential of PKIs in neurological disorders while highlighting ongoing challenges and the need for further research to refine kinase-targeted therapies.

Keywords

Protein kinases, protein kinase inhibitors, neurodegenerative diseases, psychiatric diseases, therapeutic targets, small molecules

Introduction

Neurological disorders, including neurodegenerative diseases, neuroinflammatory conditions, psychiatric disorders, neurodevelopmental diseases, and other conditions such as epilepsy, migraine, stroke, traumatic brain injury, and neurooncological disorders, represent a substantial global health burden. These disorders affect millions of individuals worldwide, resulting in severe cognitive, motor, and behavioral deficits. Current treatments predominantly offer symptomatic relief without halting disease progression. Neurodegenerative diseases involve the progressive loss of neurons, leading to cognitive decline and motor impairments, with existing treatments being largely symptomatic and lacking curative options, underscoring the need for novel therapeutic approaches. Neuroinflammatory disorders are characterized by immune system attacks on the central nervous system (CNS), causing inflammation and neuronal damage. Current therapies primarily focus on immune modulation, yet more targeted treatments are essential. Psychiatric disorders, driven by complex neurobiological factors, often have treatments with limited efficacy and significant side effects, highlighting the necessity for more effective, targeted therapies. The urgent need for innovative treatments is propelled by the limited effectiveness of current therapies, significant side effects, and the challenges associated with drug delivery to the CNS and disease heterogeneity.

Protein kinases constitute a vast family of enzymes integral to cellular signaling, primarily through the catalysis of phosphorylation—a pivotal regulatory mechanism that modulates protein activity, localization, and interactions. This process is crucial for various cellular functions, including growth, differentiation, metabolism, and apoptosis. The human genome encodes over 500 protein kinases, representing approximately 2% of the entire proteome. Phosphorylation is one of the most prevalent post-translational modifications, essential for regulating protein function [1]. Notably, around 13,000 human proteins, accounting for about 20% of all human proteins, have identified phosphorylation sites [2]. In the nervous system, kinases play a vital role in controlling neurotransmitter release, synaptic plasticity, and neuronal survival. Dysregulated kinase activity plays a key role in the pathogenesis of numerous neurological disorders, making kinases attractive therapeutic targets for addressing a wide spectrum of these conditions [3–5].

Protein kinase inhibitors (PKIs) include a wide range of chemical compounds, which can be categorized broadly into the seven district groups based on their mechanisms of action and target binding modes [6, 7] (Table 1). PKI holds significant promise in modifying disease trajectories, extending beyond mere symptomatic relief. Predominantly utilized in oncology, where the majority of clinically approved PKIs are employed, recent advancements in understanding kinase structure and function have reinforced their potential application in neurological disorders [1, 8]. The principles and strategies developed for cancer treatment, such as structure-guided drug design and the identification of resistance mechanisms, can be adapted to create CNS-penetrant PKIs. As research continues to elucidate the complex roles of kinases in the brain, the development of selective PKIs is poised to offer new therapeutic avenues for neurological disorders, addressing both symptoms and underlying pathologies. Currently, 82 PKIs are approved for clinical or preclinical study [9], with 37 specifically investigated for neurological diseases [10]. These inhibitors target signal transduction pathways, intersecting with key hub protein kinases such as Abelson kinase I (ABL1), mammalian target of rapamycin complex 1 (mTORC1), extracellular signal-regulated kinase 1/2 (ERK1/2), p38 mitogen-activated protein kinase (p38-MAPK), glycogen synthase kinase 3β (GSK3β), and protein kinase C (PKC), which are implicated in various neurological disorders. This review aims to elucidate the effects of these hub kinases and their inhibitors (Table 2), providing a conceptual framework for their potential therapeutic roles in neurodegenerative, psychiatric, and selected disorders, including autism spectrum disorders (ASD) and epilepsy.

Table 1. Categorization of protein kinase inhibitors

Category	Mechanism	Type of binding	Example
Type I	Bind to the ATP-binding site of kinases in their active conformation in their active conformation (DFG-in)	Reversible	Crizotinib (ALK inhibitor) and dasatinib (Src, ABL inhibitor [11])
Type I½	Binds to the ATP-binding pocket while extending into adjacent regions, stabilizing an intermediate conformation (DFG-in, C-helix out)	Reversible	lapatinib (EGFR, ErbB2 inhibitor [12])
Type II	Binds to the kinases in the inactive conformation (DFG-out)	Reversible	imatinib (ABL inhibitor [13]) and sorafenib (multikinase inhibitor: b-Raf, VEGF, PDGF inhibitor [14])
Type III	Act allosterically by binding to regions outside the ATP-binding site, influencing kinase activity without directly competing for ATP	Reversible	Trametinib, MEK inhibitor [15]
Type IV	Substrate-directed inhibitors modulate kinase activity by targeting regions distinct from the ATP-binding site without overlapping with Type III inhibitors	Reversible	mTORC inhibitors, everolimus [10, 16] and sirolimus [17, 18]
Type V	Bivalent inhibitors that interact with both the ATP-binding site and additional structural motifs unique to specific kinases	Reversible	Compounds targeting Src family kinases [19]
Type VI	Covalently bind to reactive residues, typically cysteines, in the ATP-binding pocket	Mostly irreversible	Afatinib (EGFR, ErbB2, ErbB4 inhibitors [20]) and neratinib (ErbB2, HER2 [21])
Type VII	Nonclassical allosteric inhibitors that target extracellular domains of receptor tyrosine kinases	Mostly irreversible	SSR128129E targeting fibroblast growth factor receptor (FGFR) family [22] and WRG-28 which inhibits the discoidin domain receptors (DDRs) [23]

ALK: anaplastic lymphoma kinase; ABL: Abelson kinase; EGFR: epidermal growth factor receptor; ErbB2: erythroblastic leukemia viral oncogene homolog 2; MEK: mitogen-activated protein kinase kinase 1/2; mTORC: mammalian target of rapamycin complex; WRG-28: *N*-Ethyl-4-[[(3-oxo-3H-phenoxazin-7-yl)oxy]methyl]-benzenesulfonamide

Table 2. Overviewed protein kinase inhibitors

Kinase	Inhibitor(s)	Targeted diseases	Reference(s)
ABL1	Imatinib, Nilotinib, Bosutinib, GNF-2, Asciminib	AD, PD, NPC, ALS	[24–32]
CaMKII	DY-9836, ST101, KN-93	AD, VD, SZ, MDD, PTSD	[33–35]
CK1δ	IGS-2.7	PD, AD, ALS	[36–41]
JNK	SP600125, FMU200, IQ-1S, PT109, Natural compounds (Emodin, Quercetin, Curcumin), Brimapitide, CEP1347	AD, PD, HD	[42–54]
CDK5	Roscovitine, ginsenoside Rg1, Quercetin, P5, Tamoxifen (TMX), LDN-193594, TFP5, pyrrolidine-2,3-dione, Luteolin, Olomoucine, 25-106	AD, PD, SZ, MDD	[55–69]
DYRK1A	DYR219, DYR533, CX-4945, PST-001, Varlitinib, ZDWX-25, EGCG, Harmine, b1	DS, AD, ALS, HD	[70–77]
ERK1/2: via MEK	SL327, PD98059, U0126	AD, PD, ALS, HD, depression, anxiety, LID	[78–84]
	PD0325901	Epilepsy	[85]
ERK1/2:	Mirdametinib (PD325901)	ASD	[86, 87]
via PDE4	Rolipram	HD, depression	[88, 89]
	Quetiapine	Depression	[90]
GSK3β	L803-mts, Lithium, AR-A014418, Tideglusib	AD, PD, HD, ALS, BD, epilepsy, SZ, depression	[91–102]
	TDZD-8, SB216763, SAR502250	Depression	[103–105]
	AF3581	BD	[106]
mTOR	Rapamycin, Everolimus, Sirolimus	AD, PD, epilepsy, TSC, ASD, LID, FCDII	[17, 18, 107–112]
	Resveratrol, Luteolin	ASD	[113, 114]
	Curcumin	ASD, TSC model	[115]
p38-MAPK	MW069, VX-745 (neflamapimod)	AD, ALS, PD, HD, dementia with Lewy bodies	[116–123]

Table 2. Overviewed protein kinase inhibitors (*continued*)

Kinase	Inhibitor(s)	Targeted diseases	Reference(s)
PKA: via PDE4	Zatomilast®	AD	[124–126]
PKC	Bryostatin-1, TMX, Myricitrin	AD, SCA, BD, mania	[127–138]
RIPK1	Necrostatin-1 (Nec-1s), DNL747	ALS, AD, HD, PD	[139–141]
ROCK1 and ROCK2	Fasudil, Ripasudil	AD, PD, HD, ALS	[142, 143]
DLK	GDC-0134	ALS, AD	[144, 145]
LRRK2	DNL201, DNL151, BIIB094	PD	[146–154]

ABL1: Abelson kinase I; CaMKII: calmodulin-dependent kinase II; CK1δ: casein kinase 1δ; JNK: c-Jun N-terminal kinase; CDK5: cyclin-dependent kinase; DYRK1A: dual-specificity tyrosine-phosphorylated and regulated kinase 1A; ERK1/2: extracellular signal-regulated kinase 1/2; MAPK: mitogen-activated protein kinase; MEK: MAPK kinase 1/2; PDE4: phosphodiesterase 4; GSK3β: glycogen synthase kinase 3β; mTOR: mammalian target of rapamycin; PKA: protein kinase A; PKC: protein kinase C; RIPK1: receptor-interacting serine/threonine protein kinase 1; ROCK1: Rho-associated protein kinases 1; DLK: dual leucine zipper kinase; LRRK2: leucine-rich repeat kinase 2; EGCG: epigallocatechin-3-gallate; AD: Alzheimer's disease; PD: Parkinson's disease; NPC: Niemann-Pick type C; ALS: amyotrophic lateral sclerosis; VD: vascular dementia; SZ: schizophrenia; MDD: major depressive disorder; PTSD: post-traumatic stress disorder; HD: Huntington's disease; ASD: autism spectrum disorder; LID: L-DOPA-induced dyskinesia; DS: Down syndrome; BD: bipolar disorder; TSC: tuberous sclerosis complex; FCDII: focal cortical dysplasia type II; SCA: spinocerebellar ataxia

ABL1

ABL1 plays a critical role in neurodegenerative diseases [155–160]. In Alzheimer's disease (AD), ABL1 regulates neuronal death in response to amyloid-beta (Aβ) fibrils, and imatinib, the ABL1 kinase inhibitor effectively reduces the cognitive deficits, Aβ oligomers, Tau phosphorylation, caspase-3 activation, neuroinflammation, and synaptic density reduction caused by monomeric Aβ [161–163]. Saracatinib, an inhibitor of ABL kinases and Src family kinases, showed promising results in preclinical studies. However, it was withdrawn during phase 2 trials due to a lack of demonstrated benefit [164]. In Parkinson's disease (PD), ABL1 phosphorylates α-synuclein and Parkin [24, 25], the disease's genetic risk factors. ABL1 deletion and inhibition protect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity and reduce α-synuclein aggregation [26, 155, 157]. Despite ABL1 kinase inhibitors (Nilotinib, Bosutinib, Imatinib) evoked disease stabilization in the PD mouse model, no significant clinical improvement was reported [27–29]. ABL1 has been implicated in amyotrophic lateral sclerosis (ALS) pathogenesis by phosphorylating transactive response DNA-binding protein 43 (TDP-43), which leads to its mislocalization and may contribute to its aggregation, a hallmark of ALS [30, 165]. ABL1 activation contributes to the impairment of autophagy, while in Niemann-Pick type C (NPC) disease, this dysfunction exacerbates the accumulation of lipids and leads to neuronal cell death [166]. Imatinib and other ABL1 inhibitors have also shown potential benefits in NPC disease and ALS [167, 168]. In ALS models, imatinib, combined with sodium channel blockers and antioxidants, prevents neuronal death [168]. Promising alternatives to imatinib are novel allosteric inhibitors of ABL1, like GNF-2 and asciminib, though their impact on neurodegenerative diseases remains unexplored [31, 32].

Calmodulin-dependent kinase II

Dysregulation of calmodulin-dependent kinase II (CaMKII) signaling is linked to both neurodegenerative and psychiatric disorders. In AD and mild cognitive impairment (MCI), altered CaMKII activity correlates with cognitive decline, with decreased phosphorylated CaMKIIα in dendrites and synapses and increased phosphorylation in perikarya in hippocampal neurons [169, 170]. Elevated CaMKIIα expression and autophosphorylation in AD brains are associated with tau hyperphosphorylation at multiple ser/the sites and neurofibrillary tangle (NFT) formation [170–172]. CaMKIIα competing with postsynaptic density protein 95 (PSD-95) for binding to the *N*-methyl-*D*-aspartate (NMDA) receptors influences neuronal survival [173, 174]. CaMKII inhibition reduces Aβ-induced caspase activity and tau phosphorylation, mitigating neuronal decline [33]. CaMKII dysregulation is also involved in vascular dementia (VD), influencing vascular smooth myocytes and endothelial function [175–177]. DY-9836, a calmodulin

inhibitor, restoring CaMKII phosphorylation, improved memory in models of VD, emphasizing its therapeutic potential [34].

CaMKII expression is altered in schizophrenia (SZ) and major depressive disorder (MDD). Elevated CaMKIIβ mRNA levels are found in the prefrontal cortex (PFC) of SZ and MDD patients, though post-mortem studies reveal reduced α- and β-CaMKII protein levels, correlating with impaired NMDA receptor function in SZ [178, 179]. In animal models, the CaMKII activator ST101 improves SZ like behaviors [180]. Notably, six mutations in CaMKIIα have been identified in SZ, impairing its biochemical functions and contributing to intellectual disabilities [181, 182]. Enhancing CaMKII activity may address social and cognitive impairments linked to SZ, which often resist traditional antipsychotic treatments [180]. The CaMKII inhibitor KN-93 has shown potential by reducing D2 receptor states in the striatum, elevated in SZ [35]. In MDD, CaMKIIβ is upregulated in the lateral habenula (LH) and hippocampus, with antidepressants reversing this effect [183, 184]. Conversely, reduced CaMKIIα expression in the PFC is observed in both MDD patients and mouse post-traumatic stress disorder (PTSD) models [185, 186].

Casein kinase 1δ

Overexpression and aberrant casein kinase 1δ (CK1δ) activity contributes to hyperphosphorylation and aggregation of α-synuclein, tau, Parkin, and TDP-43, advancing the progression of PD, AD, and ALS [187–191]. Mutations in CK1δ are linked to circadian rhythm disturbances, also observed in AD and ALS [192–195]. CK1δ inhibitors, like IGS-2.7, reduce TDP-43 toxicity and prevent neuronal death in ALS models [36–38]. However, due to the promiscuity of most CK1δ inhibitors, their therapeutic potential is complicated [39–41].

c-Jun N-terminal kinase

c-Jun N-terminal kinase 3 (JNK3) plays a pivotal role in the pathogenesis of neurodegenerative diseases [196], contributing to oxidative stress, neuroinflammation, and synaptic dysfunction [197]. In AD, the activation of JNK3 plays a pivotal role in several pathological processes. It promotes autophagy [198], drives apoptosis, including in response to endoplasmic reticulum (ER) stress [199, 200], increases tau phosphorylation, and contributes to synaptic loss [198, 199]. Notably, elevated levels of JNK3 in the cerebrospinal fluid (CSF) of AD patients suggest its potential as a biomarker for the disease [201]. Additionally, JNK3 regulates synaptic plasticity and enhances the production of Aβ, further exacerbating Aβ-induced synaptopathy [202–205]. JNK3 has emerged as a therapeutic target in AD. JNK inhibitors, SP600125 and FMU200, show neuroprotective and cognitive benefits [42, 43]. In PD, JNK3 drives apoptosis and autophagy [44], while necrostatin-1 (Nec-1s), a blocker of receptor-interacting serine/threonine protein kinase 1 (RIPK1), an upstream JNK regulator, shows neuroprotective effects [45]. SP600125, a selective JNK inhibitor, has been shown to protect dopaminergic neurons (DAs) in a sub-acute MPTP model of PD [46]. In Huntington's disease (HD), JNK inhibition prevents axonal transport disruption and reduces brain lesions [47, 48].

Currently, numerous promising JNK3 inhibitors emerge: IQ-1S offers neuroprotection [49], and PT109 promotes hippocampal neurogenesis [50]. Natural compounds like Emodin, Quercetin, and Curcumin also show JNK3 inhibitory effects [51, 52]. Peptide inhibitors like Brimapitide and upstream inhibitor CEP1347 are under investigation in AD and PD trials [53, 54].

Cyclin-dependent kinase

Cyclin-dependent kinase (CDK5) is a crucial kinase involved in the pathogenesis of neurodegenerative diseases. In AD, it enhances Aβ generation and mitochondrial neurotoxicity [206, 207]. Non-selective CDK5 inhibitors, such as Roscovitine and Ginsenoside Rg1, effectively reduce Aβ formation [55]. CDK5 is also vital in NFT formation [56], while Quercetin, the truncated peptide P5, and Tamoxifen (TMX, anti-cancer drug) inhibiting CDK5-p25 activity, block pathological tau phosphorylation [57–59]. Dual inhibition of CDK5 and GSK3β might be beneficial, as shown by LDN-193594, to improve memory in CDK5-p25 mouse models

[208, 209]. Neuroprotection was shown by traditional Chinese medicine compounds, Nano-HO and Kaixinsan by inhibiting the CDK5-GSK3β pathway in AD models [60, 61]. Other novel CDK5 pathway regulators (TFP5 and pyrrolidine-2,3-dione) are under investigation [62–64]. In PD, dysregulation of CDK5 is linked to DA loss [34, 210–213], while CDK5 inhibitors and compounds like luteolin show neuroprotective effects [65, 66]. CDK5 inhibitors have not yet been tested as specific therapies for HD.

The synaptic hypothesis of SZ and MDD implicates CDK5 in the dysregulation of neuroplasticity and neurotransmitter release [214, 215]. CDK5 suppresses neurotransmitter release [216]. The CDK5 inhibitor, Roscovitine, increases DA release and modulates glutamatergic transmission, crucial to SZ pathophysiology [67]. Antipsychotic treatments downregulate CDK5/p35/p25 levels supporting CDK5's involvement in SZ [217]. CDK5/p35 phosphorylates priming and SNARE-complex proteins affecting vesicle fusion and neurotransmitter release [218, 219], while antipsychotic treatment in SZ patients reduces the levels of these proteins [220]. Elevated CDK5 levels in the basolateral amygdala (BLA) are associated with increased anxiety, and the CDK5 inhibitor, Olomoucine, reduces anxiety when infused into the BLA [68, 221]. Another CDK5 inhibitor, 25-106, has demonstrated anxiolytic effects in mice [69]. Nevertheless, no CDK5 inhibitor has been approved for neuropsychiatric or neurodegenerative disease treatment [69].

Dual-specificity tyrosine-phosphorylated and regulated kinase 1A

Dual-specificity tyrosine-phosphorylated and regulated kinase 1A (DYRK1A) is implicated in several neurological diseases, including AD, Down syndrome (DS), and ASD [222]. Elevated DYRK1A levels are associated with increased tau phosphorylation, leading to hyperphosphorylation of amyloid precursor protein (APP). This process elevates Aβ40 and Aβ42 levels, contributing to β-amyloidosis and neuroinflammation, which exacerbates neurodegeneration [223–226]. Mutations that disrupt DYRK1A function are linked to the pathophysiology of ASD [227], while haploinsufficiency can lead to a DS-like phenotype in mice [228]. Additionally, DYRK1A promotes α-synuclein phosphorylation and cytoplasmic aggregation, which enhances its pro-apoptotic effects, contributing to PD, Lewy body dementia, and multiple system atrophy [229–231]. As a therapeutic target, several DYRK1A inhibitors are being investigated: DYR219 and DYR533 show promise in mitigating degeneration and behavioral deficits [70–72]; CX-4945, PST-001, and Varlitinib are effective in reducing tau phosphorylation [73]; and ZDWX-25 has been shown to enhance learning and memory [74]. Moreover, epigallocatechin-3-gallate (EGCG) and harmine have demonstrated improvements in cognitive deficits [75]. A novel 6-hydroxybenzothiazole urea derivative, b1, protects against α-synuclein aggregation and 6-OHDA-induced cell death [76]. Harmine prevents neurotoxicity in HD [77].

ERK1/2

Abnormal activation of the ERK1/2 pathway contributes to neurodegeneration. ERK1/2 signaling dysregulation, driven by tissue-type fibrinogen activators, NMDA receptors, and PKC-related pathways, contributes to NFT formation in AD via triggering GSK3β activation [232, 233]. ERK1/2 also affects APP processing, influencing Aβ plaque formation [234, 235]. In PD, ERK1/2 mediates oxidative stress in microglia, contributing to DA neuron degeneration [236, 237]. Moreover, ERK1/2 is involved in L-DOPA-induced dyskinesia (LID), while ERK1/2 inhibition by SL327 reduces symptoms [78]. In the $SOD1^{G93A}$ ALS mouse model, highly phosphorylated ERK1/2 [238] in microglia are linked to depletion of TDP-43, leading to increased cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE2) production [239, 240] and NOX2 pathway activation participating in oxidative stress [241]. In HD, ERK1/2 activating transcriptional responses and inhibiting pro-apoptotic factors provides a neuroprotective effect [242, 243]. Pharmacological targeting of ERK1/2 mainly involves its upstream regulators, mitogen-activated protein kinase kinase 1/2 (MEK1/2). MEK1/2 inhibitors, such as PD98059 and U0126, show high specificity and efficacy in AD and ALS models [79, 80]. Additionally, the phosphodiesterase 4 (PDE4) inhibitor rolipram, which activates ERK1/2, has shown benefits in HD models [88, 89].

Dysregulation of ERK1/2 signaling is a key factor in mood disorders, including depression. Chronic stress reduces ERK1/2 activity in the PFC, contributing to depressive-like behaviors [81], and direct inhibition of ERK1/2 induces depression-like symptoms [244–246]. Chronic pharmacological inhibition of ERK with the MEK inhibitor, U0126, leads to anhedonia and anxiety-like behaviors [82]. Conditional knockout of ERK2 results in social behavior deficits, while ERK2 overactivation reduces depression-like behaviors, reversed by the MEK inhibitor SL327 [83, 84]. Antidepressants counteract phosphorylated ERK1/2 decline in the frontal cortex and hippocampus, alleviating depression-like symptoms [247, 248]. Quetiapine combined with transcranial magnetic stimulation (TMS) restores ERK1/2 phosphorylation and exhibits antidepressant effects [90]. MEK inhibitors, U0126 and SL327, block the effects of antidepressant drugs, highlighting the crucial role of ERK in mediating these effects [81]. The ERK pathway activates transcription factors like ETS (E26 transformation-specific) like-1 protein (Elk-1) and cAMP response element-binding protein (CREB), bridging surface membrane signals with genomic responses and influencing antidepressant action [249, 250].

Dysregulation of ERK1/2 contributes to epilepsy. Seizures rapidly increase phosphorylated ERK1/2 (pERK1/2) levels, reflecting its involvement in hyperexcitability. Prolonged ERK1/2 activation is observed in various seizure models [85, 251, 252]. Notably, MEK-ERK inhibitors like PD0325901 reduce seizure activity by decreasing pERK1/2 levels, showing therapeutic potential for epilepsy [85]. The ERK pathway is also implicated in ASD, particularly in "Rasopathies" like Neurofibromatosis Type 1 and Noonan syndrome, which involve mutations in ERK signaling [86]. Dysregulated ERK signaling is linked to ASD traits in models like Fragile X Syndrome and the 16p11.2 deletion. MEK inhibitors such as PD325901 (Mirdametinib) show promise by crossing the blood-brain barrier (BBB), reducing abnormal dendritic patterning, and improving social behaviors in animal models of ASD [86, 87]. These findings highlight the potential of ERK inhibitors for treating epilepsy, ASD, and related conditions.

GSK3β

GSK3β is a key kinase implicated in neurodegeneration. In AD, GSK3β abnormal activity leads to tau hyperphosphorylation [253], amyloidogenic processing of APP, and increasing Aβ production [254, 255] that contributes to cognitive decline and neuronal damage, making GSK3β inhibition a promising therapeutic approach for AD [256, 257]. GSK3β inhibitors, like L803-mts, restore lysosomal function and reduce Aβ aggregation [91]. In PD, GSK3β dysregulation contributes to DA neuron death and α-synuclein aggregation [258]. Inhibitors such as lithium and AR-A014418 exhibit neuroprotective effects in PD models, preventing neuron degeneration and reducing neuroinflammation [92, 93]. In HD, GSK3β exacerbates neuronal dysfunction through huntingtin (Htt) phosphorylation. GSK3β inhibitors exhibit neuroprotective effects, including clearing mutant Htt aggregates and improving motor functions in HD models [94, 95]. In ALS, elevated GSK3β levels are linked to TDP-43 phosphorylation and cytoplasmic accumulation [259]. Tideglusib and other GSK3β inhibitors have shown promise in reducing TDP-43 levels and improving motor function [96]. Substrate competitive inhibitors (SCIs) for GSK3β, mimicking substrates to act as potent inhibitors, have therapeutic potential across AD, PD, and multiple sclerosis by providing targeted inhibition [91, 97, 98].

The PI3K/AKT/GSK3 pathway is crucial in psychiatric disorders. Alterations in the PI3K pathway, such as changes in the catalytic subunit p110 and SNPs in the p85 regulatory subunits, are associated with SZ and alcohol-related behaviors [260, 261]. AKT1 is linked to SZ [262–264], while AKT2 and AKT3 are implicated in anxiety, depression, and SZ [265–269]. GSK3β dysfunction is notably associated with bipolar disorder (BD) and SZ [267, 270]. GSK3β is involved in mood regulation and depressive disorders, with increased GSK3β activity correlated with BD and depression [271, 272]. Notably, several PKIs targeting GSK3β have shown promise. Lithium, a well-known mood stabilizer, inhibits GSK3 signaling and enhances AKT activity [99–101]. Recent studies highlight that non-ATP-competitive inhibitors like TDZD-8 can reverse depressive-like behaviors [103], while ATP-competitive inhibitors such as SB216763 improve antidepressant responses in animal models [104]. SAR502250 has also been shown to alleviate stress-induced impairments [105]. Furthermore, substrate-competitive GSK3β inhibitors, including L803-mts

[102], and highly selective inhibitors like AF3581 [106], are emerging as effective therapeutic options, demonstrating the potential to reduce BD symptoms, including depressive and aggressive behaviors.

GSK3β is a promising target for epilepsy therapy. It plays a key role in regulating neuronal activity and seizure susceptibility. GSK3β affects voltage-gated sodium channels (Nav1.2, Nav1.6), crucial for neuronal excitability and plasticity, thereby influencing seizure thresholds [273, 274]. GSK3β regulates potassium channels like Kv4.2 and KCNQ2, modulating neuronal excitability through phosphorylation [275]. It impacts P/Q-type Cav2.1 calcium channels, influencing synaptic transmission [276]. Additionally, GSK3β affects α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by phosphorylating the GluA1 subunit, impacting receptor trafficking and synaptic plasticity [277]. It also modulates NMDA receptor surface localization, balancing AMPAR/NMDAR activity, which is critical for synaptic transmission [278]. GSK3β further influences GABAergic synapses by phosphorylating gephyrin, affecting GABA receptor clustering and the excitatory/inhibitory balance [279]. Its involvement in serotonergic and α7-nicotinic acetylcholine receptors also highlights its role in mood regulation and seizure modulation [280]. PKIs targeting GSK3β have the potential to modulate these pathways, making them promising therapeutic candidates for epilepsy and mood disorders.

mTOR

Dysregulation of the PI3K/AKT/mTOR pathway is linked to changes in brain size and structure, where hyperactivation leads to neuronal hypertrophy and inhibition impairs growth [281–283]. Given the central role of mTORC1 in regulating cellular processes, its inhibitors have broad effects across various neurological diseases. In AD mouse models, enhancing PI3K/AKT/mTOR signaling improves cognitive decline, while mTOR inhibition with rapamycin, repurposed for clinical trial in AD, reduces Aβ and tau pathology and reverses cognitive deficits [10, 107, 108]. This underscores the need for balanced mTOR signaling for synaptic plasticity and cognition [4, 16]. In PD, mTORC1 activity is neuroprotective [284, 285], but rapamycin improves LID [109]. While rapalogs offer less optimal brain exposure [286], ATP-competitive mTOR inhibitors are promising but face challenges with BBB permeability and toxicity [287]. mTOR hyperactivation is linked to epilepsy-related malformations of cortical development (MCD), known as mTORopathies, focal cortical dysplasia type II (FCDII), and tuberous sclerosis complex (TSC). In *TSC, TSC1/2* genes' mutations lead to mTOR hyperactivation, forming cortical tubers associated with seizures.

The mTOR inhibitor, everolimus, is FDA-approved for treating refractory seizures in TSC, and sirolimus has shown promise in younger patients [17, 18]. FCDII is associated with mTOR dysregulation, and mTOR inhibitors have shown potential in preventing and controlling seizures in animal models [110]. Additionally, mTORC1 hyperactivation is seen in acquired epilepsies like temporal lobe epilepsy (TLE) and post-traumatic epilepsy, where targeted mTOR inhibitors are being developed to reduce systemic side effects [111]. In ASD, hyperactivity of the PI3K/Akt/mTOR pathway impairs synaptic pruning, leading to dendritic spine excess and behavioral deficits. mTOR inhibitors like rapamycin have reversed ASD-related behaviors in models [112]. Natural mTOR inhibitors such as resveratrol and luteolin have improved behavior in ASD models [113, 114], while curcumin restored memory loss in a TSC2+/– model [115]. These findings highlight the therapeutic potential of mTOR inhibitors in both epilepsy and ASD.

Mutations causing loss of function in the phosphatase and tensin homolog (*PTEN*) gene, an upstream regulator of mTORC1, lead to mTORC1 hyperactivation and are associated with ASD, seizures, and cognitive disabilities [288–290]. Interestingly, the knockdown of rapamycin-insensitive mTORC2, which activates AKT [291], reversed behavioral and neurophysiological abnormalities linked to *PTEN* deficiency [292], suggesting a potential therapeutic role for mTORC2. mTORC2 also activates serum- and glucocorticoid-induced protein kinase 1 (SGK1) [293], which plays a crucial role in the pathogenesis of ALS, depression, and SZ by regulating components of glutamatergic neurotransmission and brain-derived neurotrophic factor (BDNF) signaling [294, 295]. Additionally, SGK1 phosphorylates tau, contributing to AD pathology [296], and phosphorylates Htt, implicating it in PD [297]. While mTORC2 appears significant in these disorders, there is currently no selective pharmacological inhibitor for mTORC2 that does not also affect

mTORC1 and other kinases. Although 11 inhibitors of SGK1 are under investigation, none have been studied in the context of neurological and psychiatric disorders [298].

p38-MAPK

The p38α/β kinases promote neurotoxicity, while p38γ shows neuroprotective effects. In AD, elevated levels of activated p38α are observed, and its inhibition prevents neurotoxic effects, including long-term potentiation (LTP) suppression and neuronal death induced by Aβ [299–303]. p38α inhibition also reduces Aβ-induced tau pathology and amyloidogenesis [304, 305]. Conversely, p38γ has a neuroprotective role by disrupting toxic tau interactions [306, 307]. In ALS, p38 activation is a key mechanism in pathogenesis, with elevated phosphorylated p38 levels in both human and mouse models [208, 308–310]. Inhibitors like MW069 have shown protection against motor neuron loss [311]. In PD, increased p38 activity contributes to DA neuron loss [116, 312, 313]. In HD, p38α/β inhibition protects neurons from polyglutamine-expanded Htt (polyQ-Htt)-induced toxicity [117], while p38 dephosphorylation is neuroprotective to striatal neurons in HD models [118]. Numerous p38-isoform-specific small-molecule inhibitors showed off-target effects [119–121]. A novel selective p38 inhibitor, VX-745 (neflamapimod), is currently in phase 2b trials for dementia with Lewy bodies and AD. This inhibitor has shown potential in reversing memory deficits and slowing disease progression [122, 123].

Protein kinase A

Protein kinase A (PKA) shows differential regulation in mood disorders. The regulatory subunit RIIβ is elevated in BD and reduced in depression [314, 315]. Key PKA substrates like CREB and BDNF are crucial for mood regulation. Disruptions in the PKA/CREB/BDNF pathway are proposed as risk factors for mood disorders [316]. PKA inhibitors, which affect LTP in the hippocampus and the amygdala, demonstrate anxiolytic effects [124]. PKA inhibition in the central amygdala reduces CREB and neuropeptide Y (NPY) levels, leading to anxiety-like behaviors and increased alcohol intake [125]. Furthermore, CDK5 and PKA show reciprocal regulation under stress conditions, with CDK5 inhibition increasing cAMP/PKA activity [317]. PKA also affects cognitive deficits in SZ through TCF4 and cortico-striatal circuits [318, 319].

In AD, enhancing cAMP levels might counteract Aβ-induced reduction in PKA activity and CREB phosphorylation [320]. PKA activation in AD models leads to neuroprotection and reduced Aβ levels [321]. The PDE4 inhibitor Zatomilast® is in phase III trials for cognitive deficits associated with AD [126].

PKC

Dysregulation of PKC signaling is intricately linked to AD [322]. PKCα and PKCε regulate non-amyloidogenic pathways and Aβ degradation, while PKCδ influences autophagy and apoptosis, exacerbating AD pathology [322, 323]. PKCδ inhibition in AD mouse models reduces β-secretase expression, lowers Aβ levels, decreases plaque formation, and improves cognitive deficits [324]. Elevated PKC levels, particularly PKCα, are found in AD brains and reactive astrocytes. PKC-mediated phosphorylation of myristoylated alanine-rich C-kinase substrate (MARCKS), GAP43, and GluA2 subunit of AMPARs contributes to early synaptic pathology [325–330]. PKCδ and PKCε enhance tau phosphorylation, while PKCα and PKCθ suppress it [331]. Despite the availability of numerous PKC inhibitors, Bryostatin-1 is the primary PKC inhibitor under evaluation for AD, with phase II trials showing cognitive improvements [127, 128]. Another neurodegenerative disease, spinocerebellar ataxia (SCA), has been linked to over 50 mutations in PKCγ [332]. PKC inhibitors have shown therapeutic potential in SCA models, preventing Purkinje cell death and promoting neurite extension [129, 130].

PKC plays a crucial role in the pathogenesis of BD, with hyperactive PKC signaling linked to manic symptoms. Mood stabilizers like lithium and valproic acid inhibit PKC activity, reducing membrane-associated PKC levels, which contributes to their therapeutic effects [131–133]. PKC activation, induced by phorbol 12-myristate 13-acetate (PMA), triggers manic-like behavior [333]. Amphetamine (AMPH)-induced

manic-like behaviors in animal models are also associated with increased PKC activity, while PKC inhibitors such as myricitrin prevent these effects [134, 135]. Clinically, the PKC inhibitor TMX has been effective in reducing acute manic symptoms in BD patients [136, 137], and its metabolite endoxifen shows comparable efficacy to valproic acid [138]. Additionally, TMX improves markers of neuronal viability in the PFC [334]. Despite promising outcomes, the therapeutic potential of PKC inhibitors in BD remains underexplored, with no advanced clinical trials currently underway.

Other kinases

RIPK1 is crucial in necroptosis and has been implicated in ALS and AD [335]. RIPK1 inhibitors like Nec-1s are protective in models of HD, ALS, and PD [139, 140]. DNL747, a potent RIPK1 inhibitor, is in phase 1b clinical trials [141].

Rho-associated protein kinases 1 (ROCK1 and ROCK2) are involved in AD, PD, HD, and ALS [336]. ROCK inhibitors, such as fasudil and ripasudil, are being tested for conditions including ALS [143].

Dual leucine zipper kinase (DLK) activates the JNK-dependent stress response, and its aberrant activation is noted in ALS and AD [337]. Selective DLK inhibitors, such as GDC-0134, reduce synaptic loss and neuronal degeneration, having the potential for prolonged administration [144]. Genentech's DLK inhibitor is in phase I trial for ALS [145].

Mutations in leucine-rich repeat kinase 2 (*LRRK2*) are linked to both sporadic and familial PD [338]. LRRK2 is crucial for vesicular and lysosomal trafficking, lysosomal maturation, and autophagy. Its deletion leads to α-synuclein accumulation without causing neurodegeneration [142, 339]. A range of LRRK2 inhibitors is being developed, including downstream GTPase modulators, allosteric inhibitors, ATP-competitive inhibitors, selective inhibitors for the *LRRK2 G2019S* mutation, and novel approaches like proteolysis-targeting chimeras (PROTACs) [146, 147] showing neuroprotective effect [148–151]. However, many LRRK2 inhibitors have exhibited significant kidney and lung toxicity, raising major safety concerns [152]. To address these issues, recent LRRK2 inhibitors such as DNL201 and DNL151, along with BIIB094 (an antisense oligonucleotide targeting LRRK2), have progressed to clinical trials, where they have shown promising tolerability and minimal toxicity [153, 154]. In addition, Sunitinib, a multi-kinase inhibitor that targets LRRK2, is being repurposed in clinical trials in PD for on-target therapeutic validation [340].

Protein kinases crosstalk in neurodegenerative and psychiatric diseases

Protein kinases exhibit significant cross-talk, where the activity of one kinase influences or regulates another, contributing to complex signaling networks involved in both neurodegenerative and psychiatric disorders. Understanding these interactions is critical for optimizing therapeutic strategies. GSK-3β is one of the central protein kinases widely implicated in both neurodegenerative and psychiatric disorders. It demonstrates significant cross-talk with a wide range of protein kinases, and some of these interactions play key roles in the pathogenesis of these diseases. For instance, the GSK-3β and mTOR pathways are tightly interlinked, with mTOR activity inhibiting GSK-3β via upstream AKT signaling [341]. In neurodegenerative disorders like AD, dysregulation in this pathway contributes to tau hyperphosphorylation and synaptic dysfunction. In psychiatric conditions such as BD, this cross-talk modulates neuroplasticity and mood stabilization. Lithium, a GSK-3β inhibitor, indirectly activates mTOR, providing a dual mechanism to enhance synaptic function. CDK5 and GSK-3β collaboratively regulate tau phosphorylation [342, 343]. Aging or prolonged overactivation of CDK5 primes GSK-3β, playing a central role in AD pathogenesis [342]. Hyperactivation of both kinases in AD promotes NFT formation. Targeting both pathways simultaneously, as with CDK5-GSK-3β dual inhibitors like LDN-193594, may enhance therapeutic efficacy [344]. In psychiatric disorders, CDK5 modulates dopaminergic signaling [216], while GSK-3β's role in mood regulation suggests potential synergy in treating SZ and BD [271, 272]. Interaction between ABL1 and CDK5 also plays a crucial role in AD pathogenesis. Aβ peptides activate ABL1, which in turn phosphorylates CDK5 at Tyr15, leading to tau phosphorylation [345, 346]. mTOR is another hub protein kinase. ERK1/2 activation is influenced by mTOR signaling through upstream PI3K/AKT pathways.

This cross-talk is critical for synaptic plasticity and cognitive function. Dysregulation in these pathways is evident in ASD and depression, where mTOR activators also enhance ERK1/2-mediated neuroplasticity [347–349]. MEK inhibitors, which modulate ERK1/2 activity, are being explored for neuroprotection in AD and mood stabilization in psychiatric disorders. Cross-talk between ERK1/2 and JNK kinases plays a role in balancing neuroprotection and apoptosis [350]. p38-MAPK and JNK1 contribute to cytoskeletal abnormalities and neurofilament aggregation in motor neurons, characteristic of familial and sporadic ALS [351, 352]. PKC and CaMKII regulate neurotransmitter release and synaptic plasticity through overlapping pathways. Cross-talk between these kinases is implicated in SZ and AD, where CaMKII enhances NMDA receptor signaling while PKC influences AMPA receptor trafficking. Dual modulation of these pathways could restore excitatory-inhibitory balance in these conditions [353].

Challenges in the therapeutic application of PKIs

Despite their potential, the development of PKI therapies encounters several significant challenges (Table 3).

Table 3. Challenges and limitations of the therapeutic application of protein kinase inhibitors

Aspect	Neurodegenerative disorders	Psychiatric disorders
Disease complexity	- Heterogeneity of neurodegenerative diseases (e.g., sporadic vs familial forms).	- Psychiatric disorders have highly complex and poorly defined molecular underpinnings.
	- Multiple pathways contribute to disease progression, requiring combination therapies.	- Symptoms and etiologies overlap among disorders (e.g., bipolar disorder, schizophrenia, depression).
Blood-brain barrier (BBB)	- PKIs must effectively cross the BBB, which limits many candidate drugs.	- PKIs face similar BBB challenges but are typically needed for short to intermediate-term treatments, unlike the chronic therapies required for neurodegeneration.
	- Chronic neurodegenerative diseases require sustained drug delivery, raising concerns about toxicity and drug stability.	
Off-target effects	- Kinases are involved in numerous signaling pathways, leading to potential toxicity from off-target inhibition (e.g., cardiovascular, immune effects).	- Psychiatric patients may be more susceptible to side effects such as mood instability or cognitive impairment due to off-target effects.
Patient-specific variability	- Genetic mutations (e.g., LRRK2 in Parkinson's) exist in a subset of patients, complicating treatment generalizability.	- Lack of reliable biomarkers hampers patient stratification and target validation for kinase inhibitors.
Long-term safety	- Long treatment durations required for neurodegeneration amplify safety concerns (e.g., hepatotoxicity, immune suppression).	- Long-term safety studies are needed, especially for disorders requiring continuous maintenance therapy (e.g., bipolar disorder).

PKIs: protein kinase inhibitors; LRRK2: leucine-rich repeat kinase 2

One major hurdle in developing treatments is the BBB, which serves as a gatekeeper to protect the brain from harmful substances but also limits the delivery of therapeutic agents. Many promising drugs fail to reach the brain at therapeutic concentrations due to poor BBB permeability [354]. Efforts to overcome this barrier, such as nanoparticle-based delivery systems and prodrugs, have shown promise but remain largely experimental [355]. PKIs often fail due to off-target effects as kinases have conserved domains that make it difficult to selectively inhibit one without affecting others. This lack of specificity can lead to systemic toxicity or disruption of essential cellular processes, undermining their therapeutic potential. Moreover, the interconnected nature of signaling networks in the brain means that inhibiting one pathway can inadvertently activate compensatory mechanisms, diminishing the drug's efficacy [356].

The timing of intervention is another critical factor. Most neurodegenerative diseases are diagnosed only after significant neuronal loss has occurred, limiting the potential for therapies to reverse the damage. By the time symptoms become apparent, the brain has often suffered extensive structural and functional deterioration. Current diagnostic tools, while improving, frequently fail to detect these diseases in their earliest, most treatable stages. This late-stage intervention has been a major reason for the failure of disease-modifying therapies in clinical trials. Adding to these difficulties is the incomplete understanding of the underlying disease mechanisms. Preclinical models, particularly animal models, have provided invaluable insights but often fail to replicate the full complexity of human neurodegenerative diseases. This

translational gap highlights the need for better models and a more nuanced understanding of human disease biology. Patient variability further complicates drug development. Neurodegenerative diseases are not uniform; they are influenced by a combination of genetic, environmental, and lifestyle factors. These genetic differences, along with variations in disease progression, make it unlikely that a single treatment will work for all patients. A one-size-fits-all approach has repeatedly failed, underscoring the need for personalized medicine tailored to individual patient profiles. The challenges extend to clinical trial design. Many trials rely on endpoints that may not be sensitive enough to detect early therapeutic effects, such as cognitive scores or motor assessments. The heterogeneity of patient populations further complicates trials, often leading to inconclusive results. Additionally, the adaptive nature of the brain's signaling pathways means that even when a target is successfully inhibited, compensatory mechanisms can undermine the therapeutic benefit [357].

Despite these daunting obstacles, the field is moving forward. Researchers are increasingly exploring combination therapies that target multiple aspects of disease pathology simultaneously, recognizing the multifactorial nature of neurodegenerative disorders. Advances in biomarker research are enabling earlier and more accurate diagnosis, as well as the ability to stratify patients based on their genetic and molecular profiles. Precision medicine approaches are becoming central to treatment development, allowing therapies to be tailored to the unique characteristics of each patient. Innovative technologies are also opening new doors. Gene therapies and antisense oligonucleotides offer targeted approaches for diseases with clear genetic causes, such as familial ALS and HD. Advanced drug delivery systems, including BBB-penetrating nanoparticles, are addressing longstanding challenges in CNS drug delivery. Meanwhile, high-throughput drug screening and artificial intelligence are accelerating the identification of new therapeutic candidates.

Conclusions

PKIs are increasingly recognized as promising therapeutic agents for a range of neurological disorders, both neurodegenerative and psychiatric. These inhibitors target critical signaling pathways that are often disrupted in these conditions, opening new avenues for treatment. In neurodegenerative diseases like AD, PD, and ALS, PKIs address key pathological features. For instance, targeting pathways such as ABL1, CaMKII, CK1δ, JNK, CDK5, GSK3β, and ERK1/2 has shown potential in mitigating tau hyperphosphorylation, Aβ accumulation, and synaptic dysfunction—hallmarks of these diseases. ABL1 inhibitors like imatinib have demonstrated cognitive and neuroprotective benefits in preclinical models, although clinical outcomes have been mixed. Similarly, CaMKII and CK1δ inhibitors have shown promise in reducing neurotoxicity associated with AD and ALS. Inhibitors of JNK and CDK5 offer neuroprotection by addressing apoptosis and tau pathology, while GSK3β and ERK1/2 inhibitors are being explored for their roles in managing tau-related pathology and synaptic dysfunction. In psychiatric disorders, PKIs target pathways crucial for neuroplasticity and neurotransmitter regulation. These include CaMKII, CDK5, ERK1/2, GSK3β, and PKC. For example, CaMKII inhibitors may improve cognitive and social impairments in SZ, while CDK5 inhibitors have shown anxiolytic effects in anxiety models. The ERK1/2 pathway, essential for antidepressant efficacy, is influenced by inhibitors that could modulate depressive-like behaviors. GSK3β inhibitors, such as lithium, have demonstrated mood-stabilizing effects in BD and antidepressant-like effects in preclinical studies. PKC inhibitors are also being evaluated for their potential to reduce manic symptoms in BD. In the context of epilepsy and ASD, inhibiting the GSK3, ERK1/2, and mTORC1 pathways presents a promising therapeutic strategy. GSK3 inhibitors can modulate ion channel function and receptor trafficking, while ERK inhibitors have shown potential in reducing seizure activity and addressing ASD-related behaviors. mTOR inhibitors, already in clinical use for epilepsy, may also benefit ASD patients by restoring normal synaptic pruning and improving related behavioral deficits.

Looking ahead, PKIs hold significant potential for advancing the treatment of neurological disorders. Ongoing research must continue to validate their efficacy and safety through rigorous clinical trials, with a focus on optimizing their specificity for targeted pathways. Despite their promise, the development of PKI

therapies faces several key challenges. These include the need for allosteric inhibitors to improve selectivity and reduce the risk of off-target effects, enhancing the ability of these inhibitors to cross the BBB through innovative drug delivery methods, and developing combination therapies that target multiple kinases or incorporate PKIs alongside other treatments. By addressing these challenges, PKIs could lead to new, effective treatment options, ultimately improving outcomes for patients with neurological and psychiatric disorders.

Abbreviations

ABL1: Abelson kinase I

AD: Alzheimer's disease

ALS: amyotrophic lateral sclerosis

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

APP: amyloid precursor protein

ASD: autism spectrum disorder

Aβ: amyloid-beta

BBB: blood-brain barrier

BD: bipolar disorder

BDNF: brain-derived neurotrophic factor

BLA: basolateral amygdala

CaMKII: calmodulin-dependent kinase II

CDK5: cyclin-dependent kinase

CK1δ: casein kinase 1δ

CNS: central nervous system

CREB: cAMP response element-binding protein

DAs: dopaminergic neurons

DLK: dual leucine zipper kinase

DS: Down syndrome

DYRK1A: dual-specificity tyrosine-phosphorylated and regulated kinase 1A

ERK1/2: extracellular signal-regulated kinase 1/2

FCDII: focal cortical dysplasia type II

GSK3β: glycogen synthase kinase 3β

HD: Huntington's disease

Htt: huntingtin

JNK3: c-Jun N-terminal kinase 3

LID: L-DOPA-induced dyskinesia

LRRK2: leucine-rich repeat kinase 2

LTP: long-term potentiation

MDD: major depressive disorder

MEK1/2: mitogen-activated protein kinase kinase 1/2

MPTP: methyl-4-phenyl-1,2,3,6-tetrahydropyridine

mTORC1: mammalian target of rapamycin complex 1

Nec-1s: necrostatin-1

NFT: neurofibrillary tangle

NMDA: *N*-methyl-*D*-aspartate

NPC: Niemann-Pick type C

p38-MAPK: p38 mitogen-activated protein kinase

PD: Parkinson's disease

PDE4: phosphodiesterase 4

pERK1/2: phosphorylated extracellular signal-regulated kinase 1/2

PFC: prefrontal cortex

PKA: protein kinase A

PKC: protein kinase C

PKIs: protein kinase inhibitors

PTEN: phosphatase and tensin homolog

RIPK1: receptor-interacting serine/threonine protein kinase 1

ROCK1: Rho-associated protein kinases 1

SCA: spinocerebellar ataxia

SGK1: serum- and glucocorticoid-induced protein kinase 1

SZ: schizophrenia

TDP-43: transactive response DNA-binding protein 43

TMX: Tamoxifen

TSC: tuberous sclerosis complex

VD: vascular dementia

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