RSC Medicinal Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d5md00681c

Leveraging targeted kinase degradation as a novel therapeutic strategy for Alzheimer's disease

Elisa Tassinari and Andrea Milelli *

Received 31st July 2025,
Accepted 29th September 2025

DOI: 10.1039/d5md00681c

rsc.li/medchem

Despite recent advances, Alzheimer's disease (AD) remains largely a mystery more than a century after its discovery. Protein kinases are among the new targets under investigation, which is not surprising given their crucial role in maintaining cellular homeostasis and in the development of various diseases. Several protein kinase inhibitors have shown remarkable therapeutic efficacy in the context of AD, although none of them have yet received approval by regulatory agencies. Alongside the use of classic inhibitors, a new therapeutic approach has emerged in recent years, shifting the focus from modulation to targeted degradation of the protein. The purpose of this review is to highlight and discuss novel series of proteolysis-targeting chimeras (PROTACs) directed against protein kinases relevant to the development of AD.

Introduction

More than 100 years after its discovery, Alzheimer's disease (AD) still poses formidable challenges to society and science. Indeed, AD is an age-related disease whose incidence rises significantly with increasing life expectancy.[1] In 2019, an estimated 57 million people globally were living with dementia, and the prevalence is expected to grow to 153 million people by 2050.[2] However, it should be noted that many patients with AD remain undiagnosed. From a social point of view, AD represents a huge economic burden on patients and caregivers. The estimated healthcare costs are about $305 billion in 2020 and are projected to reach $2 trillion in 2030.[3]

In addition, despite decades of substantial investment by for-profit and non-profit organizations, AD is still an unsolved question and only a few pieces of its pathogenesis are clear today.[4] Indeed, an objective understanding of its emergence and development is still far from being achieved, and many theories have been proposed in recent years by eminent scientists to explain what remains, for all intents and purposes, an enigma.[5] Due to the many theories developed, countless possible drug targets have emerged and have been pursued in numerous drug discovery programs accompanied, unfortunately, by dramatic high-level failures.[6] Up to 2021 only four molecules were used in clinical practice, three acetylcholinesterase inhibitors and one NMDA antagonist. Nevertheless, none of these drugs decrease neuronal loss or reverse cognitive impairments or act as a truly disease-modifying drug.[7] Among the various theories proposed, a central focus in the agendas of many research groups is the β-amyloid (Aβ) protein, which represents one of the two hallmarks of the disease, together with neurofibrillary tangles (NFT) consisting of hyperphosphorylated tau protein.[8] Over the years the highest efforts have been directed towards the Aβ protein and to reduce Aβ-induced toxicity. Recently, these efforts have resulted in three Aβ-directed monoclonal antibodies that have received FDA approval: aducanumab approved in 2021, albeit with furious controversy,[9] and discontinued at the beginning of 2024,[10] lecanemab[11] and donanemab.[12] Unfortunately, along with justifiable public enthusiasm, there is an animated debate in the scientific community about the efficacy, safety, and costs of these agents.[13] Indeed, these antibodies, although inducing a substantial Aβ reduction in AD patients, produce only a modest cognitive and clinical benefit compared to placebo.[14,15] In addition, numerous adverse effects were observed in the lecanemab and donanemab trials. In particular, a significant increase in cases of symptomatic amyloid-related imaging abnormalities was found during phase 3 studies.[16]

Given this, the drug discovery efforts to uncover effective disease-modifying agents for the treatment of AD are highly dynamic. According to Cummings *et al.*'s annual analysis of the AD pipeline, currently there are 182 trials and 138 novel drugs across the 2025 AD pipeline.[17] A closer look reveals that these drugs are directed towards a wide array of targets, the most common include modulators of neurotransmitter receptors, inflammation, amyloid-induced toxicity, and synaptic plasticity. Interestingly, there is an increasing number of protein kinase inhibitors in the AD pipeline,[18] which are mainly known as drugs at the forefront of the

Department for Life Quality Studies, Alma Mater Studiorum - University of Bologna, Corso d'Augusto 237, 47921 Rimini, Italy. E-mail: andrea.milelli3@unibo.it

anticancer therapy.[19] Indeed, masitinib and nilotinib BE are in clinical phase 3, while baricitinib and MW150 are in clinical phase 2.[17] However, the appearance of kinase inhibitors in the AD pipeline is not surprising considering that these proteins are responsible for the intracellular signaling and, therefore, they regulate multiple downstream effects. Several kinases play a key role in the development and progression of AD.[20] For instance, NFTs result from an overactivation of protein kinases, such as glycogen synthase kinase 3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), extracellular signal-regulated kinase 2 (ERK2), microtubule-affinity regulating kinase (MARK), protein kinase A (PKA), death-associated protein kinase 1 (DAPK1), Rho-associated protein 1 (ROCK1), and Fyn, which cause hyperphosphorylation of the tau protein and its subsequent aggregation into NFTs.[21] Besides this crucial role, kinases are also involved in other processes such as Aβ aggregation, neuroinflammation, synaptic plasticity, memory formation and overactivation of astrocytes and microglia.[20] Therefore, it is not surprising that many drug discovery programs are aimed at obtaining protein kinase inhibitors as disease-modifying agents for the treatment of AD. However, the use of kinase inhibitors for the treatment of AD is still in its infancy and, although some drugs have been or are still in the clinical study phase, there are no inhibitors that have received regulatory agency approval. Unfortunately, the development of such molecules is by no means straightforward, due to a variety of reasons, including the inherent difficulty of specifically targeting protein kinases. Off-target side effects due to poor selectivity are the main problem associated with the development of a kinase inhibitor since there are approximately 518 kinases in the human kinome. Furthermore, achieving effective therapeutic concentration in the brain is a major challenge for CNS-directed kinase inhibitors since, due to a combination of physicochemical and pharmacokinetic factors, they do not cross the blood brain barrier (BBB). Indeed, molecular weight (MW), lipophilicity ($\log P$) and polar surface area (PSA) influence the BBB penetration ability of a molecule. An analysis by Chico *et al.* reported that kinase inhibitor drugs tend to have higher mean values for these parameters, when compared to other known CNS-penetrating compounds.[22] For instance, imatinib showed limited efficacy in glioblastoma clinical trial since it did not reach therapeutic levels in the brain.[23] Lastly, since kinase networks are highly redundant and interconnected, their inhibition causes compensatory changes, thus, reducing effectiveness and causing adverse effects.

Recently, the drug design process has been disrupted by the appearance of a new strategy for modulating the activity of proteins, known as targeted protein degradation (TPD).[24] In particular, the use of proteolysis targeting chimeras (PROTACs) may offer several advantages over traditional kinase inhibitors in modulating kinase activity in AD.[25]

In the current review, to avoid unnecessary overlap with the prolific recent literature, in the following paragraph, we will briefly discuss PROTAC characteristics. Following this, we will examine the role that different kinases play in the pathogenesis of AD and highlight selected case studies of kinase-targeted PROTACs in the context of AD.

Proteolysis targeting chimeras (PROTACs)

Traditionally, small molecules, which form the basis of modern medicine, modulate the activity of a specific biochemical target through occupancy-driven pharmacology. This approach involves binding to a protein of interest (POI) to affect its functions. A revolutionary approach to control protein functions uses small molecules as "chemical inducers of proximity".[26] These molecules act by inducing spatial proximity between two proteins, ultimately leading to the modulation of the POI. Numerous classes of proximity-inducing modulators have been developed so far, with a different mode of action (MoA), leading to fascinating biochemical effects.[24] A major part of proximity-inducing modulators hijacks the cellular quality control machinery to selectively degrade target proteins.[27] Many different TPD strategies have been developed so far, including PROTACs.[28] In particular, PROTACs have become a widely explored therapeutic modality with about 20 currently in the clinical phase,[28] with vepdegestrant (ARV-471), an estrogen receptor degrader, reached phase 3 for the treatment of breast tumors.[29] Although oncology remains the main field of application for PROTACs, several promising examples of protein degraders directed against neurodegenerative disorders are emerging.[30] For instance, Arvinas recently reported ARV-102, currently under investigation in phase 1 clinical studies.[31] ARV-102 is a novel investigational oral PROTAC designed to cross the blood–brain barrier and target Leucine-rich repeat kinase 2 (LRRK2), a kinase that plays a critical role in Parkinson disease and progressive supranuclear palsy.[32] ARV-102 was generally safe and well tolerated with no serious adverse events reported. The administration of ARV-102 achieved more than 50% reduction of LRRK2 levels in the cerebrospinal fluid (CSF) at single oral dose greater at least equal to 60 mg and repeated doses of at least 20 mg.[31]

Further, LRRK2 has been the target of a successful medicinal chemistry campaign that led to the discovery of XL01126, a promising PROTAC exhibiting remarkable oral bioavailability and BBB penetration.[33]

Although no degraders for AD have entered the clinical trials yet, the development of protein degraders is extremely dynamic, as shown in Fig. 1a.[34]

Although the MoA of PROTACs is still being investigated, it is widely accepted that PROTACs initiate the degradation cascade by recruiting POI and forming a ternary complex with E3 ligase. The induced proximity between POI and E3 ubiquitin ligase causes ectopic ubiquitination of the POI, which is then degraded *via* the ubiquitin-proteasome system (UPS).

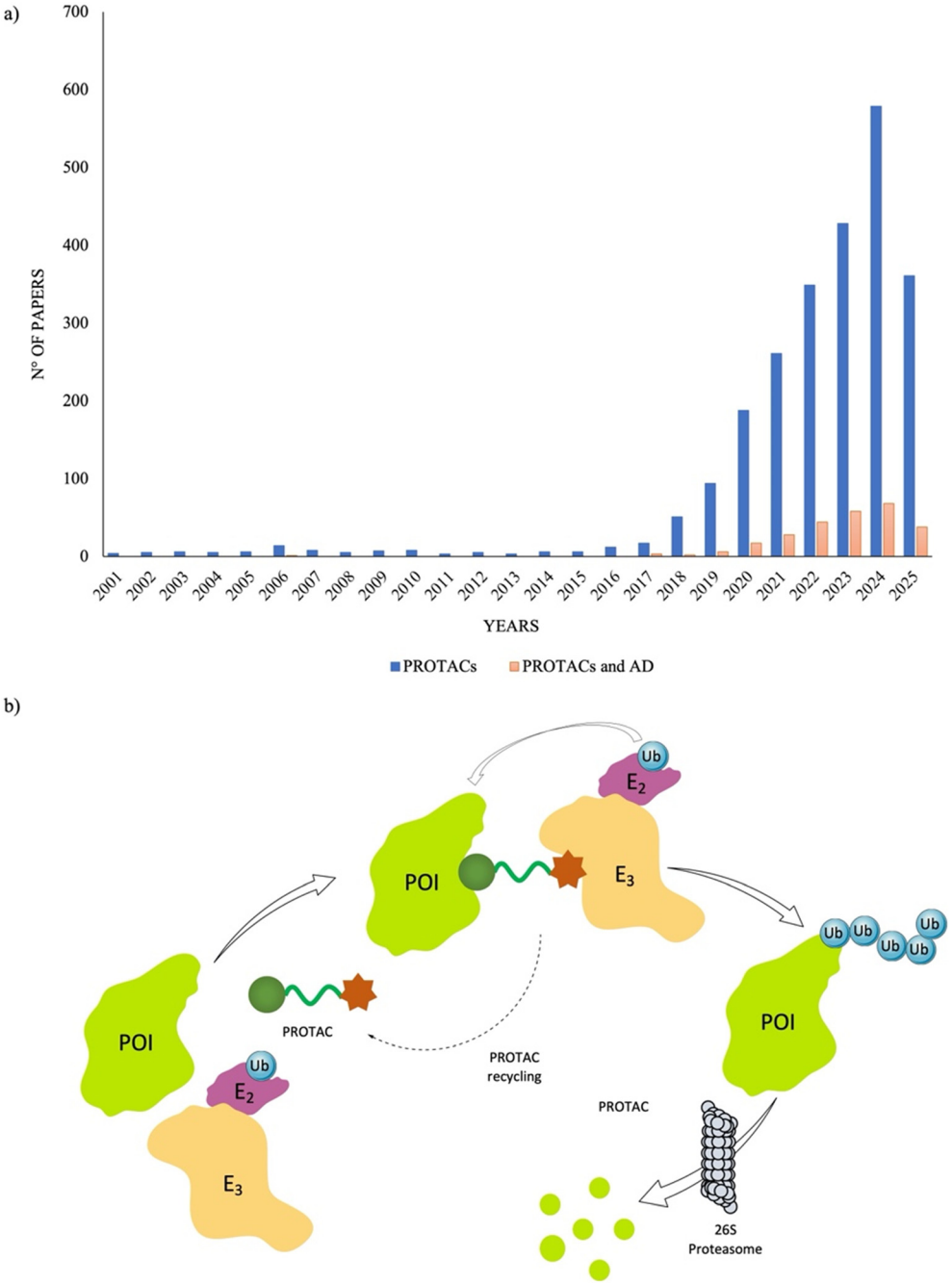

Fig. 1 a) Number of articles per year featuring "PROTACs" and "PROTAC" and "Alzheimer's disease" in the title, abstract, or keywords (Scopus search, June 2025); b) mechanism of action of PROTACs.

One of the main challenges in producing a successful kinase inhibitor lies in the identification of a potent and selective molecule able to modulate a given target. This is even more complex when dealing with protein lacking a specific binding site. Moreover, when considering classic inhibitors, it is required to maintain a suitable drug concentration for a specific amount of time. Due to their peculiar mechanism of action, PROTACs offer numerous advantages over classical small molecule inhibitors, especially regarding the treatment of brain-related diseases. Target occupancy is a crucial factor when considering classic inhibitors. To achieve sufficient level of target-occupancy, high drug concentrations are required, which are frequently associated to off-target effect(s). On the other hand, protein degradation represents an event-driven pharmacology, where a low level of target engagement may be sufficient to induce the substantial degradation of target protein.[35] Indeed, it is possible to observe EC_{50} values substantially lower compare to K_d.[36] Moreover, PROTACs, and related protein degraders, are characterized by a catalytic mode of action, that allows

protein levels to decrease more significantly over time. Consequently, complete removal of the protein from the cell is achieved, resulting in a more long-lasting effect compared to classic inhibitors.

Furthermore, classic inhibitors block enzymatic functions by binding to the catalytic domain. However, non-enzymatic functions, that play roles in regulating several disease-associated cellular pathways, are non-affected by traditional inhibitors. PROTACs, and related protein degraders, eliminate all the functions of a given protein, both enzymatic and non-enzymatic, leading to improved potency and, possibly, new mechanisms of pharmacological activities.[37]

PROTACs are less susceptible to resistance from point mutations in the target protein, a common event when dealing with kinase modulation.[30] Nevertheless, also with TPDs resistance mechanisms have been observed, such as: a) alterations in E3 ligase pathways, *i.e.* mutation or downregulation of E3 ligases, disrupting the formation of the ternary complex needed for protein degradation;[38] b) deubiquitinase enzyme overexpression, causing insufficient levels of ubiquitinated POI;[39] c) upregulation of drug efflux pumps, *i.e.* MDR1 pump and ABCC1/MRP1.[40,41]

From a medicinal chemistry's point of view PROTACs are relatively simple heterobifunctional molecules comprising two different warheads, one for POI recruitment and the other one for binding to a specific E3 ligase. The two heads are connected by a linker, that is critical for the correct formation of a productive ternary complex[42,43] and for modulating solubility and cell penetration.[44] There are numerous factors to take into consideration when designing a successful PROTAC, such as selecting the right POI recruiter, the correct linker as well as the suitable ligase. The discussion of these aspects is beyond the scope of this mini-review therefore, for a more detailed discussion of these aspects, the reader is referred to these excellent papers.[27,28,45–47]

Glycogen synthase kinase 3β (GSK-3β)

GSK-3β is a highly conserved serine/threonine kinase ubiquitously expressed and constitutively active. Although it was initially known only for its role in glycogen metabolism, it is now recognized as a central node in multiple signaling pathways involved in maintaining correct cell homeostasis. In particular, regarding its CNS-related roles, it plays a crucial role in neuronal development where it regulates neurite outgrowth in adult, synapse formation and plasticity and neurogenesis.[48] In CNS, GSK-3β is the most abundant isoform and its expression levels are known to increase with age[49] and it is found to be hyperactivated in the brain of AD patients. Compelling evidence indicates that GSK-3β is the primary tau kinase involved in AD's pathology.[50] It is well known that GSK-3β plays a central role in the production of NFTs, which are composed of hyperphosphorylated tau protein.[50] The affinity of tau protein for microtubules is mainly dependent on its phosphorylation status and GSK-3β-mediated hyperphosphorylation induces its dissociation from microtubules and its aggregation to give NFTs. GSK-3β is also involved in Aβ-induced toxicity since it regulates amyloid precursor protein (APP) processing.[51] Indeed, GSK-3β enhances the activity of both β-secretase (BACE-1) and γ-secretase, which are responsible for the proteolytic cleavage of APP. This increases the production of Aβ peptides, which then aggregate to form Aβ plaques. Moreover, GSK-3β is expressed in both microglia and astrocytes where it promotes the production of inflammatory cytokines, such as IL-1, IL-6, and TNF-α and may contribute to a chronic inflammatory state.[52,53] Compelling evidence also indicates that GSK-3β activation contributes to cognitive deficits in AD since it plays a key role in synaptic plasticity and memory formation.[54] Considering this, numerous molecules capable of modulating GSK-3β activity have been developed over the years and some of them have reached the clinical phase.[55] For instance, tideglusib, an orally active non-ATP competitive GSK-3β inhibitor, in a first pilot study showed a significant improvement in cognition compared to placebo-patients.[56] However, in a phase IIb trial, although it was well tolerated, no significant improvements were detected.[57] Similarly, long-term treatment with lithium significantly reduced phospho-tau levels in cerebrospinal fluid (CSF) and improved cognitive parameters in patients with mild cognitive impairment (MCI).[58] Moreover, microdoses of lithium for 15 months successfully decreased cognitive decline in AD patients.[59] However, it is important to point out that a recent paper reported that lithium deficiency is a potential common mechanism for the multisystem degeneration of the brain that leads to the onset of AD and, consequently, the pharmacological effects observed in lithium treatments may not be solely attributed to GSK-3β inhibition.[60]

In recent years, alternative approaches to modulate GSK-3β have been very successful, including development of GSK-3β-directed multi-target drugs.[61] Alongside, some GSK-3β-directed PROTACs have been discovered showing extremely exciting anti-AD properties (Fig. 2).[62–65]

In 2021, Jiang *et al.* reported the design, synthesis, and biological evaluation of a series of PROTACs based on thalidomide, as cereblon (CRBN) ligand, and the pyridinethiazole-based inhibitor **1**,[66] which is a highly potent and selective ATP competitive GSK-3β inhibitor.[62] Among the different analogs, a promising GSK-3β degrader, PG21, was obtained following an extensive campaign of linker optimization (Fig. 2). PG21, characterized by an octamethylene linker, showed dose-dependent GSK-3β-degradation, resulting in a 44.2% reduction in the enzyme levels at 2.8 μM, relying on the ubiquitin–proteasome system (UPS) mechanism. Interestingly, other PEG-linked analogs exhibited no significant activity. PG21 exhibited good selectivity for GSK-3α/β enzymes among 18 kinases, as well as anti-inflammatory effects in mouse BV2 microglial cells treated with Lipopolysaccharide (LPS). It significantly

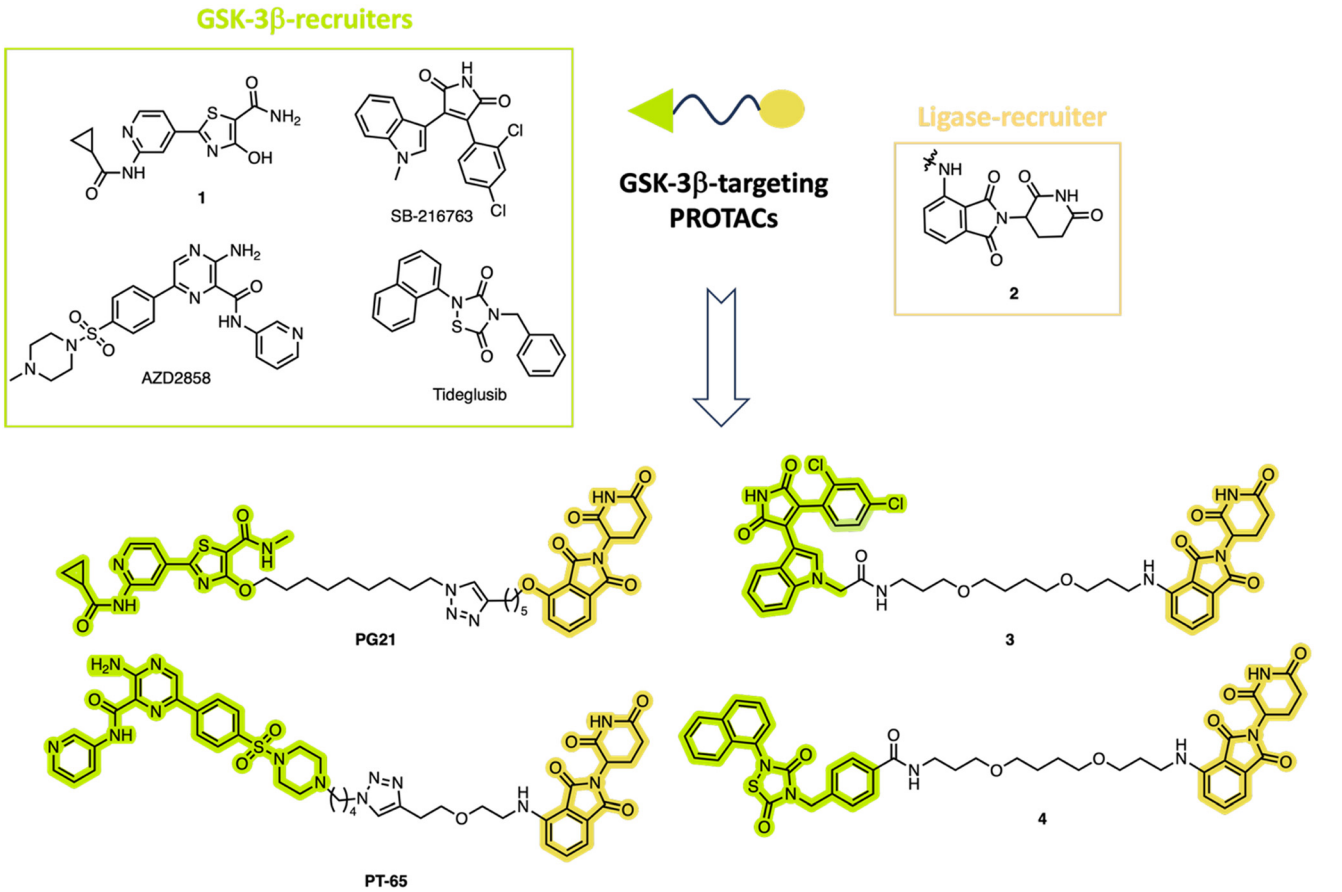

Fig. 2 Design of GSK-3β-directed PROTACs. GSK-3β recruiting elements are highlighted in light green, while ligase-recruiting elements are highlighted in light orange.

reduced the expression of the pro-inflammatory cytokine TNF-α, which is related to several human diseases, including AD.[67] In addition, PG21 prevented glutamate-induced cytotoxicity in HT-22 hippocampal neuronal cells, suggesting a neuroprotective role that preserves cellular morphology and neuronal integrity.

The same year, Wang and co-workers discovered PT-65, a potent GSK-3β degrader, which exhibited DC_{50} values of 28.3 nM and 34.2 nM against GSK-3α and GSK-3β in SH-SY5Y cells, respectively (Fig. 2).[63] AZD2858, a potent and selective competitive ATP inhibitor,[68] was selected as GSK-3β warhead while pomalidomide was chosen as CRBN ligand. PT-65 shows a high affinity for GSK-3β (K_D = 12.41 nM), with only about a twofold decrease compared to AZD2858, indicating its notable degradation potency. Further evaluations were conducted to explore the mechanism of degradation of PT-65. Pre-treatments of SH-SY5Y cells with pomalidomide and MG-132, a known proteasome inhibitor, markedly attenuated PT-65-induced GSK-3 degradation, suggesting an UPS-mediated degradation. Moreover, the treatment with PT-65 in cells containing high levels of GSK-3β and p-Tau showed a reduction in GSK-3β and p-Tau levels in a dose-dependent manner, without altering the total level of Tau. The same treatment was conducted using AZD2858, which inhibited the enzymatic activity of GSK-3β, leading to a dose-dependent decrease in p-Tau. After removing the compounds through washing out, GSK-3β activity and p-Tau levels rapidly returned to normal in cells treated with AZD2858. On the contrary, GSK-3β took longer to recover in cells treated with PT-65. These findings underline the potential therapeutic advantages of PT-65 as a protein degrader in the treatment of AD, due to its longer duration of efficacy and, consequently, a potential reduced number of administrations. Furthermore, PT-65 reduced Aβ-induced tau hyperphosphorylation and neurotoxicity in SH-SY5Y cells, a common cellular model for AD, increasing cell viability in a dose-dependent manner with no observed toxicity up to 100 μM. Moreover, PT-65 can improve learning and memory impairment on AD model rats induced by administration of okadaic acid (OA). Indeed, the compound showed a reduction in the escape latency in the Morris water maze (MWM) test, indicating cognitive improvement, and a decreased p-Tau and GSK-3α/β expression in the hippocampus.

In 2023, our research group reported a small set of novel GSK-3β degraders based on PROTAC technology. This involved linking two different GSK-3β inhibitors, SB-216763 and tideglusib, which weren't previously explored in degraders, to pomalidomide, selecting different-length PEG

linkers.[64] The study also aimed to evaluate potential differences in ATP- and non-ATP-competitive GSK-3β recruitment. Indeed, SB-216763 is a selective reversible maleimide-based ATP competitive inhibitor of GSK-3β while tideglusib is a selective GSK-3β inhibitor that acts *via* a non-ATP competitive mechanism.[69] While derivatives of tideglusib, such as compound **4**, did not exhibit appreciable degradation of the POI, the SB-216763 derived compounds did show significant decrease in the GSK-3β level. However, the lack of activity is unlikely to be related to the allosteric binding: a more plausible explanation lies in the linker design, which plays a critical role in ternary complex formation.[43] Compound **3**, characterized by the SB-216763 warhead and the 3–4–3 PEG linker, emerged as the most potent degrader of the set inducing GSK-3β degradation, due to the formation of a more stable ternary complex (Fig. 2). This was demonstrated also by the docking analysis, which showed that a longer linker allowed the pomalidomide to reach the β-hairpin loop of the kinase, encouraging the binding with CRBN. The inhibitory profile of compound **3**, evaluated through Kinase-Glo luminescent assay, seemed sufficient to engage GSK-3β. PROTAC **3** exhibited an IC_{50} of 833 nM, a value that is more than one order of magnitude higher compared to the starting inhibitor itself (SB-216763 IC_{50} = 34 nM). However, one of the critical differences between PROTACs and classic inhibitors is that for PROTACs a moderate binding to the POI is sufficient to trigger the degradation process. PROTAC **3** showed no neurotoxicity in SH-SY5Y cell lines up to 20 μM and induced significant degradation starting from 0.5 μM in a dose dependent manner. As in previous studies, the involvement of the UPS system in the degradation of GSK-3β was also demonstrated by using lactacystin, a specific proteosome inhibitor. PROTAC **3** significantly reduced the neurotoxicity induced by $A\beta_{25-35}$ peptide and $CuSO_4$ in SH-SY5Y cells in a dose-dependent manner. Since the ability to cross the blood–brain barrier (BBB) is notably important for AD-drugs, PROTAC **3** was evaluated through PAMPA BBB assay, exhibiting an effective permeability (P_e) of about 15.33. This classifies PROTAC **3** as CNS± permeable, approaching CNS+, *i.e.* it exhibits a moderate ability to cross the BBB, with a value not far from the optimal one for crossing the BBB.

It is well known that PROTACs physicochemical properties remain a significant challenge, especially in the CNS PROTAC landscape.[70] In this context, Holmqvist *et al.* demonstrated that the use of orthogonally reactive linkers enables the identification of CNS *in vivo* active degraders of GSK-3β from a single screen (Fig. 3).[65] The orthogonally reactive linkers method leads to a rapid and selective combination of the POI ligand and the E3 ligase binder, based on the fact that during the assembly one end of the linker reacts exclusively with the POI binder and the other end only with the E3 ligase recruiter, without any disruption. Therefore, the orthogonally reactive linker binds selectively and independently the GSK-3β ligand and the E3 ligase recruiter, avoiding cross-reactivity and/or unwanted side reactions that can occur with standard linkers. This approach enables the synthesis of multiple combinations, resulting in a large library of compounds and substantially increasing the probability of identifying molecules with good degradation activity and suitable physicochemical properties. In this context, the authors selected 12 non-excessive polar and non-long orthogonal reactive linkers presenting an alkyne group and a secondary amine: first the secondary amine undergoes an SN2

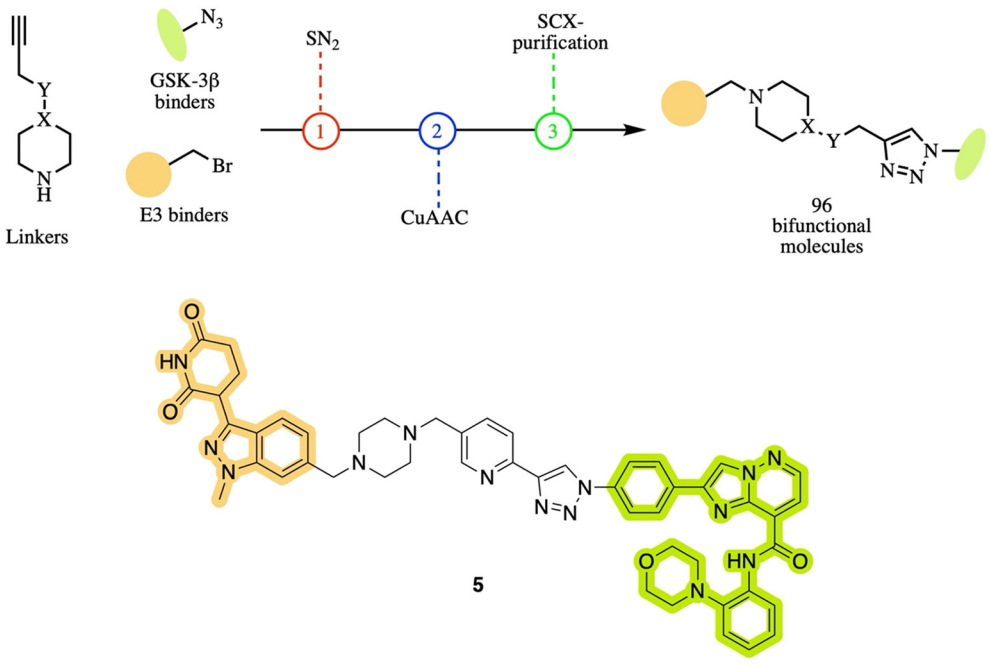

Fig. 3 Synthetic sequence and structure of compound **5**.

with a bromine-containing E3-ligase recruiter and, second, the alkyne reacts with an azido-containing POI binder *via* click chemistry (Fig. 3). As GSK-3β-recruiters, the authors selected two different binders, PT-367 and CMP-47,[71] both modified by the addition of an azido group. The CRBN-recruiting fragments were selected based on minimal molecular weight and high hydrolytic stability. The synthesis was performed in a 96-well plate, starting with the SN2 reaction followed by the click reaction. A different plate was used for the two selected GSK-3β ligands, with the seven different E3 binders distributed in rows and the twelve linkers in columns. The plates were purified using a 96-well strong cation exchange (SCX) plate, facilitated by the presence of the basic center in the linkers, which encourages the separation of non-reacted species and by-products from the desired PROTACs. 103 of the 147 compounds obtained exhibited >50% of purity when detected in LC-MS. The compounds were directly screened through a direct-to biology strategy[72] to evaluate the ability of crude compounds to degrade GSK-3β in GSK-3β-HiBiT knock-in HEK293 cell lines after 24 h treatment. Six compounds emerged, exhibiting a good degradation profile and were subsequently re-synthesized and purified *via* preparative HPLC to compare the degradation efficacy. The DC_{50} values left shifted from 2.5 to 20 folds from the crude to the purified compound, confirming that all DC_{50} values were lower than 20 nM. In particular, compound **5** was selected for further evaluation (Fig. 3). It degrades GSK-3β and GSK-3α after a 2 hour-treatment with a 10 nM concentration, and its selectivity to GSK-3 paralogs was confirmed by tandem-mass-tagging. Furthermore, they investigated the effects of GSK-3 degradation on the level of β-catenin and on collapsin response mediator protein 2 levels (CRMP2), which are hyperphosphorylated in the brain of AD patients. Compound **5**, after a 24 hour-treatment in SH-SY5Y cells, induced no phosphorylation in β-catenin up to 100 nM, whereas p-CRMP2 levels were decreased at already 0.1 nM. Moreover, in mice 5 mg kg^{-1} i.v. of compound **5** leads to a complete GSK-3β elimination in liver and a partial remotion in mouse brain within 4 hours, attributing to **5** good potentialities and confirming the reliability of the use of orthogonally reactive linkers and a direct-to biology approach to accelerate new SNC PROTACs discovery.

Mitogen-activated protein kinase family member p38α (p38α MAPK)

p38α MAPK is rapidly emerging as central regulator of inflammation, tau pathology, neuronal death, and synaptic dysfunction in AD.[73] It belongs to a family of stress-activated serine/threonine kinases, where the α is the isoforms more implicated in AD. Indeed, it is predominant in neurons and glial cells.[74,75] It is one of the main kinases responsible for the hyperphosphorylation of the tau protein. Interestingly, p38α MAPK not only directly phosphorylates tau protein, but it is also able to activate other kinases, such as MAPK-activated protein kinase 2 (MK2), which in turn modulates tau phosphorylation.[76] MW181, a brain-permeable small molecule inhibitor of p38α MAPK, decreased tau phosphorylation in an hTau transgenic mouse model of AD and significantly improved working memory in rodents.[77] In addition, it has been observed that p38α MAPK plays an important role in the production of Aβ plaques. Specifically, p38α MAPK influences the expression and activity of BACE-1, a key enzyme in the amyloidogenic pathway that cleaves APP to produce Aβ.[78] Many studies have revealed the deep involvement of p38α MAPK in the production of inflammatory cytokines leading to chronic inflammation. Interestingly, Aβ has also been identified as a stimulus activating p38 MAPK cascades for the production and upregulation of pro-inflammatory cytokines in microglia.[79] Moreover, p38α MAPK is also involved in astrocytic iNOS and TNF-α production resulting in chronic neuroinflammation.[80,81] Furthermore, p38α MAPK plays a significant role in modulating synaptic plasticity.[82] Indeed, it impairs long-term potentiation (LTP) leading to synaptic loss, reduced dendritic spine density and impaired learning and memory.[82] Therefore, p38α MAPK have gained attention as potential therapeutic agents for the treatment of AD due to their ability to modulate neuroinflammation, tau pathology, and synaptic dysfunction. Several different inhibitors have been developed[83] and neflamapimod showed improved memory performance in early AD patients in a phase 2a trial.[84]

In 2023, Son *et al.* reported a direct selective degradation of phosphorylated-p38 (p-p38), the p38 active form, by exploiting the glycine flip-intrinsic conformation of the activated p-p38.[85] According to this, a series of PROTACs have been designed by selecting the previously reported p38 benzophenone inhibitor **6**, which targets the glycine flip,[86] and pomalidomide, which acts as an E3 ligase binder, connected *via* linker of various types and lengths (Fig. 4). Among them, compound **7** emerged as the most potent p-p38 degrader since it exhibited higher selectivity for the activated p-p38 compared to the non-phosphorylated counterpart, as

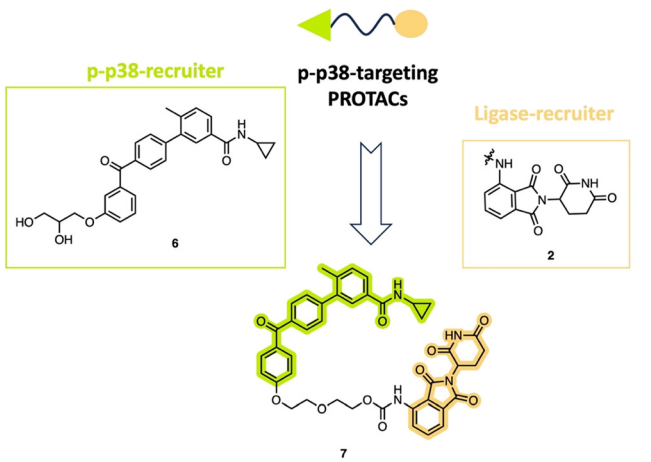

Fig. 4 Design of p38α MAPK-directed PROTAC. p38α MAPK recruiting elements are highlighted in light green, while ligase-recruiting elements are highlighted in light orange.

confirmed by docking studies and degradation assays performed on various neuronal cells, such as mouse astrocytes (C8-D1A), mouse neuroblasts (N2a) and mouse hippocampal neuronal cells (HT22). Furthermore, compound 7 selectively targets p-p38, significantly reducing its level, compared to a panel of 96 kinases sharing a similar function and/or structure with p38. Additionally, the phosphorylation state of upstream MAPK kinases (MAPKKs), which is responsible for the p-38 activation, is not affected by compound 7, confirming its selectivity.

The degradation activity of compound 7 depends on its interaction with CRBN, as p-p38 degradation was hindered when cells were treated with the compound lacking the pomalidomide moiety. This highlights the crucial role of pomalidomide in inducing the effect. Furthermore, treatment with MG-132 decreased the degradation rate of p-p38, whereas inhibition of the lysosomal pathway using chloroquine (CQ) had no effect on p-p38 levels. These findings further confirmed that the degradation was mediated through the UPS. Compound 7 proved to be able to reduce the neuroinflammation mediated by p-p38, which plays an important role in the regulation of proinflammatory responses by promoting the mRNA expression of pro-inflammatory cytokines. Treatment of BV-2 microglial cells with increasing concentrations of compound 7 significantly decreased the levels of IL-6, IL-8, IL-12 and TNF-α in a dose-dependent manner. In contrast, the p38 mRNA level remained unchanged, as proof that suppression of the neuroinflammation depends on a degradation mechanism rather than the inhibition of p38 synthesis.

Intranasal administration of compound 7 suppressed Aβ deposition-induced neuroinflammation in 5xFAD mice aged 8 to 9 months old, showing a notable reduction in p-p38 levels and in Aβ deposition in both cortex and hippocampus after 1 month treatment. Moreover, treatment with compound 7 improved MWM performance in terms of spatial memory and learning, suggesting beneficial effects on cognitive function. After treatment with compound 7, the level of p-Tau decreased in both the 5xFAD model and the rat AD model PS19, showing memory improvement. Taken together, these results demonstrated that compound 7 decreases Aβ deposition, p-Tau levels, and proinflammatory cytokine production by degrading p-p38, leading to pathological amelioration in AD rat model. Furthermore, the intranasal administration confirmed to be an efficient strategy to reach the CNS by bypassing the BBB, not easily penetrated by CNS-PROTACs, due to their relevant molecular weight.

Conclusions and perspective

Protein kinase inhibitors represent a first-line therapy for the treatment of several types of cancer, such as imatinib in gastrointestinal stromal tumors or osimertinib in non-small cell lung cancer.[19] Alongside this use, given the importance of kinases in brain pathophysiology, kinase inhibitors are also being explored for the treatment of brain-related diseases, such as AD. Several protein kinase inhibitors are in clinical trials for the treatment of AD, such as masitinib and nilotinib in phase 3, baricitinib and dasatinib in phase 2 and many others in phase 1.[17] These molecules block the activity of the protein by occupying the orthosteric site or, in some cases, the allosteric site. In this mini review, we aim to highlight a novel strategy to modulate the activity of protein kinases involved in the development of AD, by inducing their degradation. The application of the TPD concept, using PROTACs, molecular glues and so on, is revolutionizing the field of drug discovery in an unprecedent way.[28] As highlighted in this discussion, the application of TPD in the context of AD-related kinases is still in its infancy, especially when compared to its use in oncology. Indeed, aside from the GSK-3β and the p-p38 PROTACs reported in this work, there are no degraders targeting other kinases evaluated in the AD models. However, PROTACs directed towards other kinases involved in the pathogenesis of AD, such as Pi3K and AKT, have been reported.[87,88] Nevertheless, these PROTACs, although effective in inducing protein degradation in cells, have only been reported as antiproliferative agents and have not been evaluated in any in-cell or in *in vivo* models of AD. As matter of fact, it would be extremely interesting to assess such PROTACs in these models to fully explore the potential of targeted-kinase degradation in AD. However, we firmly believe that TPD can represent a significant step-forward in the modulation of protein kinases involved in AD, given the many advantages of protein degradation over classical inhibition. Among all different advantages associated with the use of PROTACs, a key strength in the context of brain diseases is, in our opinion, their catalytic mechanism of action, which enables therapeutic efficacy to be achieved at lower concentrations than those required for conventional inhibitors. Moreover, although PROTACs face significant challenges in crossing the BBB, their catalytic activity can partially compensate for their limited penetration. In addition, the catalytic activity of PROTACs, combined with their ability to degrade the target protein, allows for a longer duration of action than traditional inhibitors, since they remove the protein itself rather than temporarily blocking its activity.

Significant effort has already been made to target neurodegenerative disease-related proteins, such as tau, with degraders or proximity-inducing modulators.[89] However, there are several problems associated with the use of PROTACs, mainly related to their unfavorable chemical–physical properties, *i.e.* high molecular weight, high H-bond donor and acceptor number *etc.* Indeed, PROTACs usually have poor cellular permeability and oral bioavailability. Moreover, these kinase-directed PROTACs are expected to exhibit higher concentrations in the periphery than in the CNS, leading to severe on- and off-target side effects. However, these issues could be reduced by exploiting CNS-specific E3 ligases, such as RNF182[90] and tripartite motif-

containing protein 9 (TRIM9),[91] enabling tissue- and cell-type-specific target degradation. Furthermore, PROTACs optimization continues to be an empirical, and time-consuming process of "trial and error" driven by numerous iterative cycles of data collected from compound testing. Fortunately, new platforms are emerging to accelerate the process of PROTAC discovery and optimization, such as the direct-to-biology approach, which combines high-throughput chemistry with high-throughput cell-based assays.[72,92]

A boost to the research for new degraders of AD-related kinases may come from the success of the medicinal chemistry campaign that led to the discovery of ARV-102, an leucine-rich repeat kinase 2-targeting PROTAC exhibiting remarkable BBB penetration, safety and good *in vivo* degradation activity.[31]

We strongly believe that the examples herein reported clearly demonstrate encouraging potential for the treatment of neurodegenerative diseases, and we are optimistic that new studies for the treatment of AD will complement these efforts, broadening the therapeutic landscape.

Author contributions

ET: formal analysis, writing – original draft, writing – reviewing & editing. AM: conceptualization, formal analysis, writing – original draft, writing – reviewing & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

This review does not include any primary research results, software or code. No new data have been generated or analysed in any part of this review.

Acknowledgements

This work was financially supported by the Alma Mater Studiorum – University of Bologna.

References

1 G. N. Collaborators, *Lancet Neurol.*, 2019, **18**, 459–480.
2 G. D. F. Collaborators, *Lancet Public Health*, 2022, **7**, e105–e125.
3 L. X. Tay, S. C. Ong, L. J. Tay, T. Ng and T. Parumasivam, *Value Health Reg. Issues*, 2024, **40**, 1–12.
4 M. Nasb, W. Tao and N. Chen, *Aging Dis.*, 2024, **15**, 43–73.
5 J. Zhang, Y. Zhang, J. Wang, Y. Xia and L. Chen, *Signal Transduction Targeted Ther.*, 2024, **9**, 211.
6 S. Asher and R. Priefer, *Life Sci.*, 2022, **306**, 120861.
7 G. T. Grossberg, G. Tong, A. D. Burke and P. N. Tariot, *J. Alzheimers Dis.*, 2019, **67**, 1157–1171.
8 C. Ma, F. Hong and S. Yang, *Molecules*, 2022, **27**, 1210.
9 A. Mullard, *Nat. Rev. Drug Discovery*, 2021, **20**, 496.
10 **https://www.alz.org/alzheimers-dementia/treatments/aducanumab**.
11 S. Reardon, *Nature*, 2023, **613**, 227–228.
12 A. Mullard, *Nat. Rev. Drug Discovery*, 2025, **24**, 75–82.
13 P. Hunter, *EMBO Rep.*, 2024, **25**, 5227–5231.
14 The Lancet, *Lancet*, 2022, **400**, 1899.
15 T. Daly, K. P. Kepp and B. P. Imbimbo, *Alzheimer's Dementia*, 2024, **20**, 6659–6661.
16 F. J. Wolters and J. A. Labrecque, *Alzheimer's Dementia*, 2024, **20**, 3119–3125.
17 J. L. Cummings, Y. Zhou, G. Lee, K. Zhong, J. Fonseca, A. M. Leisgang-Osse and F. Cheng, *Alzheimer's Dementia*, 2025, **11**, e70098.
18 Z. Li, B. Yin, S. Zhang, Z. Lan and L. Zhang, *Eur. J. Med. Chem.*, 2023, **261**, 115817.
19 J. Li, C. Gong, H. Zhou, J. Liu, X. Xia, W. Ha, Y. Jiang, Q. Liu and H. Xiong, *Int. J. Mol. Sci.*, 2024, **25**, 5489.
20 X. Wu, Z. Yang, J. Zou, H. Gao, Z. Shao, C. Li and P. Lei, *Signal Transduction Targeted Ther.*, 2025, **10**, 146.
21 G. Montalto and R. Ricciarelli, *BioFactors*, 2023, **49**, 502–511.
22 L. K. Chico, L. J. Van Eldik and D. M. Watterson, *Nat. Rev. Drug Discovery*, 2009, **8**, 892–909.
23 P. Y. Wen, W. K. Yung, K. R. Lamborn, P. L. Dahia, Y. Wang, B. Peng, L. E. Abrey, J. Raizer, T. F. Cloughesy, K. Fink, M. Gilbert, S. Chang, L. Junck, D. Schiff, F. Lieberman, H. A. Fine, M. Mehta, H. I. Robins, L. M. DeAngelis, M. D. Groves, V. K. Puduvalli, V. Levin, C. Conrad, E. A. Maher, K. Aldape, M. Hayes, L. Letvak, M. J. Egorin, R. Capdeville, R. Kaplan, A. J. Murgo, C. Stiles and M. D. Prados, *Clin. Cancer Res.*, 2006, **12**, 4899–4907.
24 X. Liu and A. Ciulli, *ACS Cent. Sci.*, 2023, **9**, 1269–1284.
25 M. Pettersson and C. M. Crews, *Drug Discovery Today: Technol.*, 2019, **31**, 15–27.
26 C. J. Gerry and S. L. Schreiber, *Nat. Chem. Biol.*, 2020, **16**, 369–378.
27 L. Zhao, J. Zhao, K. Zhong, A. Tong and D. Jia, *Signal Transduction Targeted Ther.*, 2022, **7**, 113.
28 M. Békés, D. R. Langley and C. M. Crews, *Nat. Rev. Drug Discovery*, 2022, **21**, 181–200.
29 C. Arnold, *Nat. Med.*, 2024, **30**, 3030–3031.
30 J. A. Gregory, C. M. Hickey, J. Chavez and A. M. Cacace, *Cell Chem. Biol.*, 2024, **31**, 1688–1698.
31 **https://ir.arvinas.com/news-releases/news-release-details/arvinas-presents-first-human-data-investigational-oral-protac/**.
32 C. Zhu, S. Herbst and P. A. Lewis, *J. Cell Sci.*, 2023, **136**, jcs259724.
33 X. Liu, A. F. Kalogeropulou, S. Domingos, N. Makukhin, R. S. Nirujogi, F. Singh, N. Shpiro, A. Saalfrank, E. Sammler, I. G. Ganley, R. Moreira, D. R. Alessi and A. Ciulli, *J. Am. Chem. Soc.*, 2022, **144**, 16930–16952.
34 H. Inuzuka, J. Liu, W. Wei and A. H. Rezaeian, *Acta Mater. Med.*, 2022, **1**, 24–41.
35 I. Churcher, *J. Med. Chem.*, 2018, **61**, 444–452.
36 D. P. Bondeson, A. Mares, I. E. Smith, E. Ko, S. Campos, A. H. Miah, K. E. Mulholland, N. Routly, D. L. Buckley, J. L. Gustafson, N. Zinn, P. Grandi, S. Shimamura, G. Bergamini, M. Faelth-Savitski, M. Bantscheff, C. Cox, D. A. Gordon, R. R.

Willard, J. J. Flanagan, L. N. Casillas, B. J. Votta, W. den Besten, K. Famm, L. Kruidenier, P. S. Carter, J. D. Harling, I. Churcher and C. M. Crews, *Nat. Chem. Biol.*, 2015, **11**, 611–617.
37 D. Sun, J. Zhang, G. Dong, S. He and C. Sheng, *J. Med. Chem.*, 2022, **65**, 14276–14288.
38 L. Zhang, B. Riley-Gillis, P. Vijay and Y. Shen, *Mol. Cancer Ther.*, 2019, **18**, 1302–1311.
39 T. V. Nguyen, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2111391118.
40 A. M. Kurimchak, C. Herrera-Montávez, S. Montserrat-Sangrà, D. Araiza-Olivera, J. Hu, R. Neumann-Domer, M. Kuruvilla, A. Bellacosa, J. R. Testa, J. Jin and J. S. Duncan, *Sci. Signaling*, 2022, **15**, eabn2707.
41 G. Wolf, C. Craigon, S. T. Teoh, P. Essletzbichler, S. Onstein, D. Cassidy, E. C. H. Uijttewaal, V. Dvorak, Y. Cao, A. Bensimon, U. Elling, A. Ciulli and G. Superti-Furga, *Cell Chem. Biol.*, 2025, **32**, 291–306.e296.
42 A. Bricelj, Y. L. Dora Ng, D. Ferber, R. Kuchta, S. Müller, M. Monschke, K. G. Wagner, J. Krönke, I. Sosič, M. Gütschow and C. Steinebach, *ACS Med. Chem. Lett.*, 2021, **12**, 1733–1738.
43 D. Weerakoon, R. J. Carbajo, L. De Maria, C. Tyrchan and H. Zhao, *J. Chem. Inf. Model.*, 2022, **62**, 340–349.
44 V. Poongavanam, Y. Atilaw, S. Siegel, A. Giese, L. Lehmann, D. Meibom, M. Erdelyi and J. Kihlberg, *J. Med. Chem.*, 2022, **65**, 13029–13040.
45 S. L. Paiva and C. M. Crews, *Curr. Opin. Chem. Biol.*, 2019, **50**, 111–119.
46 M. Schade, J. S. Scott, T. G. Hayhow, A. Pike, I. Terstiege, M. Ahlqvist, J. R. Johansson, C. R. Diene, C. Fallan, A. Y. S. Balazs, E. Chiarparin and D. Wilson, *J. Med. Chem.*, 2024, **67**, 13106–13116.
47 R. I. Troup, C. Fallan and M. G. J. Baud, *Explor. Target. Antitumor Ther.*, 2020, **1**, 273–312.
48 E. Beurel, S. F. Grieco and R. S. Jope, *Pharmacol. Ther.*, 2015, **148**, 114–131.
49 S. J. Lee, Y. H. Chung, K. M. Joo, H. C. Lim, G. S. Jeon, D. Kim, W. B. Lee, Y. S. Kim and C. I. Cha, *Neurosci. Lett.*, 2006, **409**, 134–139.
50 E. Lauretti, O. Dincer and D. Praticò, *Biochim. Biophys. Acta, Mol. Cell Res.*, 2020, **1867**, 118664.
51 G. F. Chen, T. H. Xu, Y. Yan, Y. R. Zhou, Y. Jiang, K. Melcher and H. E. Xu, *Acta Pharmacol. Sin.*, 2017, **38**, 1205–1235.
52 E. E. Spangenberg and K. N. Green, *Brain, Behav., Immun.*, 2017, **61**, 1–11.
53 H. F. Green and Y. M. Nolan, *Neurochem. Int.*, 2012, **61**, 666–671.
54 P. Salcedo-Tello, A. Ortiz-Matamoros and C. Arias, *Int. J. Alzheimer's Dis.*, 2011, **2011**, 189728.
55 S. M. Arciniegas Ruiz and H. Eldar-Finkelman, *Front. Mol. Neurosci.*, 2021, **14**, 792364.
56 T. del Ser, K. C. Steinwachs, H. J. Gertz, M. V. Andrés, B. Gómez-Carrillo, M. Medina, J. A. Vericat, P. Redondo, D. Fleet and T. León, *J. Alzheimer's Dis.*, 2013, **33**, 205–215.
57 S. Lovestone, M. Boada, B. Dubois, M. Hüll, J. O. Rinne, H. J. Huppertz, M. Calero, M. V. Andrés, B. Gómez-Carrillo, T. León, T. del Ser and A. Investigators, *J. Alzheimer's Dis.*, 2015, **45**, 75–88.
58 O. V. Forlenza, V. J. De-Paula and B. S. Diniz, *ACS Chem. Neurosci.*, 2014, **5**, 443–450.
59 M. A. Nunes, T. A. Viel and H. S. Buck, *Curr. Alzheimer Res.*, 2013, **10**, 104–107.
60 L. Aron, Z. K. Ngian, C. Qiu, J. Choi, M. Liang, D. M. Drake, S. E. Hamplova, E. K. Lacey, P. Roche, M. Yuan, S. S. Hazaveh, E. A. Lee, D. A. Bennett and B. A. Yankner, *Nature*, 2025, **645**, 712–721.
61 A. De Simone, V. Tumiatti, V. Andrisano and A. Milelli, *J. Med. Chem.*, 2021, **64**, 26–41.
62 X. Jiang, J. Zhou, Y. Wang, X. Liu, K. Xu, J. Xu, F. Feng and H. Sun, *Eur. J. Med. Chem.*, 2021, **210**, 112949.
63 L. Qu, S. Li, L. Ji, S. Luo, M. Ding, F. Yin, C. Wang, H. Luo, D. Lu, X. Liu, W. Peng, L. Kong and X. Wang, *Eur. J. Med. Chem.*, 2021, **226**, 113889.
64 M. Guardigni, L. Pruccoli, A. Santini, A. Simone, M. Bersani, F. Spyrakis, F. Frabetti, E. Uliassi, V. Andrisano, B. Pagliarani, P. Fernández-Gómez, V. Palomo, M. L. Bolognesi, A. Tarozzi and A. Milelli, *ACS Chem. Neurosci.*, 2023, **14**, 1963–1970.
65 A. Holmqvist, N. M. Kocaturk, C. Duncan, J. Riley, S. Baginski, G. Marsh, J. Cresser-Brown, H. Maple, K. Juvonen, N. Morrice, C. Sutherland, K. Read and W. Farnaby, *ChemRxiv*, 2025, preprint, DOI: **10.26434/chemrxiv-2025-nq14w**.
66 P. Sivaprakasam, X. Han, R. L. Civiello, S. Jacutin-Porte, K. Kish, M. Pokross, H. A. Lewis, N. Ahmed, N. Szapiel, J. A. Newitt, E. T. Baldwin, H. Xiao, C. M. Krause, H. Park, M. Nophsker, J. S. Lippy, C. R. Burton, D. R. Langley, J. E. Macor and G. M. Dubowchik, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1856–1863.
67 W. S. Griffin and S. W. Barger, *US Neurol.*, 2010, **6**, 19–27.
68 S. Berg, M. Bergh, S. Hellberg, K. Högdin, Y. Lo-Alfredsson, P. Söderman, S. von Berg, T. Weigelt, M. Ormö, Y. Xue, J. Tucker, J. Neelissen, E. Jerning, Y. Nilsson and R. Bhat, *J. Med. Chem.*, 2012, **55**, 9107–9119.
69 A. Martinez, M. Alonso, A. Castro, C. Pérez and F. J. Moreno, *J. Med. Chem.*, 2002, **45**, 1292–1299.
70 P. Agarwal, D. L. Reid and M. Amiji, *J. Controlled Release*, 2024, **372**, 661–673.
71 R. A. Hartz, V. T. Ahuja, P. Sivaprakasam, H. Xiao, C. M. Krause, W. J. Clarke, K. Kish, H. Lewis, N. Szapiel, R. Ravirala, S. Mutalik, D. Nakmode, D. Shah, C. R. Burton, J. E. Macor and G. M. Dubowchik, *J. Med. Chem.*, 2023, **66**, 4231–4252.
72 C. E. Hendrick, J. R. Jorgensen, C. Chaudhry, I. I. Strambeanu, J. F. Brazeau, J. Schiffer, Z. Shi, J. D. Venable and S. E. Wolkenberg, *ACS Med. Chem. Lett.*, 2022, **13**, 1182–1190.
73 J. Detka, N. Płachtij, M. Strzelec, A. Manik and K. Sałat, *Molecules*, 2024, **29**, 4354.
74 P. R. Asih, E. Prikas, K. Stefanoska, A. R. P. Tan, H. I. Ahel and A. Ittner, *Front. Mol. Neurosci.*, 2020, **13**, 570586.
75 S. H. Lee, J. Park, Y. Che, P. L. Han and J. K. Lee, *J. Neurosci. Res.*, 2000, **60**, 623–631.

76 X. Zhu, C. A. Rottkamp, H. Boux, A. Takeda, G. Perry and M. A. Smith, *J. Neuropathol. Exp. Neurol.*, 2000, **59**, 880–888.
77 N. Maphis, S. Jiang, G. Xu, O. N. Kokiko-Cochran, S. M. Roy, L. J. Van Eldik, D. M. Watterson, B. T. Lamb and K. Bhaskar, *Alzheimer's Res. Ther.*, 2016, **8**, 54.
78 L. Schnöder, W. Hao, Y. Qin, S. Liu, I. Tomic, X. Liu, K. Fassbender and Y. Liu, *J. Biol. Chem.*, 2016, **291**, 2067–2079.
79 D. R. McDonald, M. E. Bamberger, C. K. Combs and G. E. Landreth, *J. Neurosci.*, 1998, **18**, 4451–4460.
80 Y. B. Lee, J. W. Schrader and S. U. Kim, *Cytokine*, 2000, **12**, 874–880.
81 N. R. Bhat, D. L. Feinstein, Q. Shen and A. N. Bhat, *J. Biol. Chem.*, 2002, **277**, 29584–29592.
82 C. Falcicchia, F. Tozzi, O. Arancio, D. M. Watterson and N. Origlia, *Int. J. Mol. Sci.*, 2020, **21**, 5624.
83 F. Yang, L. J. Zhao, Q. Xu and J. Zhao, *Eur. J. Med. Chem.*, 2024, **280**, 116950.
84 N. D. Prins, J. E. Harrison, H. M. Chu, K. Blackburn, J. J. Alam, P. Scheltens and R.-S. S. Investigators, *Alzheimer's Res. Ther.*, 2021, **13**, 106.
85 S. H. Son, N. R. Lee, M. S. Gee, C. W. Song, S. J. Lee, S. K. Lee, Y. Lee, H. J. Kim, J. K. Lee, K. S. Inn and N. J. Kim, *ACS Cent. Sci.*, 2023, **9**, 417–426.
86 J. Heo, H. Shin, J. Lee, T. Kim, K. S. Inn and N. J. Kim, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3694–3698.
87 I. You, E. C. Erickson, K. A. Donovan, N. A. Eleuteri, E. S. Fischer, N. S. Gray and A. Toker, *Cell Chem. Biol.*, 2020, **27**, 66–73.e67.
88 W. Li, C. Gao, L. Zhao, Z. Yuan, Y. Chen and Y. Jiang, *Eur. J. Med. Chem.*, 2018, **151**, 237–247.
89 E. Uliassi, M. L. Bolognesi and A. Milelli, *ACS Pharmacol. Transl. Sci.*, 2025, **8**, 654–672.
90 Q. Y. Liu, J. X. Lei, M. Sikorska and R. Liu, *Mol. Neurodegener.*, 2008, **3**, 4.
91 S. Menon, D. Goldfarb, C. T. Ho, E. W. Cloer, N. P. Boyer, C. Hardie, A. J. Bock, E. C. Johnson, J. Anil, M. B. Major and S. L. Gupton, *Mol. Biol. Cell*, 2021, **32**, 314–330.
92 Z. Wang, S. Shaabani, X. Gao, Y. L. D. Ng, V. Sapozhnikova, P. Mertins, J. Krönke and A. Dömling, *Nat. Commun.*, 2023, **14**, 8437.