

Targeted Protein Degraders for Central Nervous System Drug Discovery: BBB Permeability, Pharmacokinetics, And Delivery Challenges

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Abstract

Targeted protein degradation (TPD) has emerged as a promising strategy for eliminating disease-associated proteins that are difficult to modulate using conventional inhibitors. Among its major approaches, proteolysis-targeting chimeras (PROTACs) and molecular glue degraders have gained attention in neurodegenerative disease research. However, translating these degraders into effective central nervous system (CNS) therapies is challenging because the blood–brain barrier (BBB) restricts brain exposure and many degraders possess physicochemical and pharmacokinetic properties that are unfavourable for CNS delivery. This review examines the key factors governing CNS-targeted protein degradation, with emphasis on BBB permeability, molecular size, lipophilicity, polarity, hydrogen bonding, flexibility, brain exposure and unbound drug concentrations. Pharmacokinetic behaviour, PK–PD relationships and emerging delivery approaches, including nanocarriers, receptor-mediated transport, intranasal administration and exosome-based systems, are also discussed. In addition, in-silico strategies involving target and E3-ligase selection, ternary-complex modelling, molecular dynamics, BBB permeability and ADMET prediction are considered for early degrader optimization. Preclinical studies involving tau, α -synuclein and DAPK1 demonstrate the potential of TPD in neurodegenerative disorders, although effective and selective degradation within the brain remains a major translational challenge. Overall, successful CNS protein degradation will require integrated optimization of degrader structure, brain exposure, pharmacokinetics, delivery and intracellular target engagement.

Keywords: Targeted protein degradation; PROTAC; molecular glue; central nervous system; blood–brain barrier; pharmacokinetics; CNS delivery; in-silico evaluation; neurodegenerative diseases.

Introduction

Central nervous system (CNS) disorders remain difficult to treat because effective therapy requires both suitable biological targets and delivery of active drugs to the appropriate brain region and cell type. This is particularly relevant to neurodegenerative diseases, where pathogenic proteins contribute to progressive neuronal dysfunction. Targeted protein degradation (TPD) offers an alternative to conventional approaches by reducing the abundance of disease-associated proteins and has therefore gained interest in CNS drug discovery.[1], [2]

TPD promotes selective removal of intracellular proteins by engaging cellular degradation machinery. The major approaches are proteolysis-targeting chimeras (PROTACs) and molecular glue degraders. PROTACs are heterobifunctional molecules containing a target-binding ligand and an E3 ubiquitin ligase ligand connected by a linker, promoting ubiquitination and subsequent proteasomal degradation. Molecular glues achieve a similar outcome by inducing or stabilizing target–E3

ligase interactions without the conventional PROTAC architecture.[2], [3]

The potential of TPD in neuroscience lies in its ability to eliminate selected proteins rather than simply inhibit their function. Degradation effects may persist beyond direct drug–target binding, supporting investigation of TPD against neurological and neurodegenerative disease-associated proteins, including targets that are difficult to modulate with conventional inhibitors.[2], [3]

However, translation of TPD into CNS therapeutics is limited by the blood–brain barrier (BBB), which restricts brain entry of many systemically administered compounds. The large and complex structures of many degraders may further affect permeability, polarity, solubility, metabolic stability and pharmacokinetics. Effective CNS degradation therefore requires consideration of molecular properties and brain exposure in addition to target potency.[1]

This review discusses the major challenges in developing targeted protein degraders for CNS drug discovery, focusing on BBB permeability, physicochemical and pharmacokinetic properties, brain exposure, computational evaluation and emerging delivery strategies. Current progress and key translational challenges in achieving effective and selective protein degradation within the CNS are also considered

Targeted Protein degradation in CNS drug discovery

Targeted protein degradation (TPD) redirects cellular degradation machinery toward selected proteins, reducing their abundance rather than

continuously blocking their function. Most intracellular TPD approaches use the ubiquitin–proteasome system through recruitment of an E3 ubiquitin ligase, expanding opportunities to address targets that are difficult to inhibit conventionally.[4], [5]

PROTACS

Proteolysis-targeting chimeras (PROTACs) are heterobifunctional degraders composed of a target-binding ligand, an E3-ligase ligand and a connecting linker. They promote formation of a target–PROTAC–E3 complex, leading to target ubiquitination and proteasomal degradation. Their event-driven or catalytic behaviour distinguishes them from conventional inhibitors and supports investigation in neurological disorders. [4], [6]

For CNS applications, PROTACs must combine effective target and E3-ligase engagement with suitable cellular entry, systemic exposure and brain access. E3-ligase selection is also important because expression can vary across CNS regions and cell types, making brain-enriched or disease-relevant ligases potential opportunities for improved selectivity. [4], [6]

Molecular glue degraders

Molecular glues provide another TPD approach. These generally smaller monovalent molecules induce or stabilize interactions between an E3 ligase and target protein, resulting in ubiquitination and degradation. Their compact structure may offer more drug-like physicochemical properties than many PROTACs, although identifying suitable glues and achieving target and E3-ligase selectivity remain challenging. [4], [7]

Table 1: Source: Adapted and Synthesized from Kuemper et al.(2024) and related literature.

Feature	PROTACS	Molecular Glue Degraders
Basic structure	Bifunctional	Usually monovalent
Target binding	Target ligand required	Often induced/stabilized interaction
E3 ligase recruitment	E3 ligand	Direct/induced E3 interaction
Linker	Usually present	Generally absent
Molecular size	Usually larger	Generally smaller

CNS relevance	BBB penetration challenging	Potentially more favourable physicochemical properties
Main advantage	Rational modular design	Compact structure and potentially improved drug-like properties
Major limitation	Size, polarity, flexibility	Discovery and selectivity challenges

Relevance of TPD to CNS Drug Discovery

Growing preclinical evidence supports TPD against neurological disease-associated proteins, including α -synuclein and tau. These studies demonstrate the potential of degradation to address pathological protein accumulation, although most CNS degrader programmes remain preclinical and require further optimization of brain exposure, pharmacokinetics and safety. [8]

Blood–Brain Barrier and CNS Permeability of Targeted Protein Degraders

The blood–brain barrier (BBB) is a specialized interface between blood and brain that maintains a controlled environment for neuronal function. Brain microvascular endothelial cells form its main restrictive component through tight junctions, with support from pericytes, astrocytes and other neurovascular-unit components. Transport proteins also regulate molecular entry and removal. While essential for brain protection, the BBB substantially limits delivery of therapeutic agents to the CNS. [9], [10]

Brain entry depends on a molecule's physicochemical properties and interaction with BBB transport systems. Passive diffusion generally favours molecules with suitable size, lipophilicity and limited polarity, whereas carrier-mediated transport and receptor-

mediated transcytosis provide alternative routes. Efflux proteins such as P-glycoprotein (P-gp) and BCRP can reduce brain exposure by returning susceptible compounds to the circulation. Thus, CNS permeability reflects the combined effects of influx, passive movement and efflux. [9], [11]

These limitations are particularly important for targeted protein degraders. Heterobifunctional degraders are often larger and more flexible than conventional CNS drugs, and their size, polarity, hydrogen bonding and conformational flexibility can limit BBB penetration. Efflux interactions may further reduce exposure. However, measurable brain penetration has been reported for some degraders, suggesting that CNS activity depends on coordinated optimization of molecular structure, transport behaviour and pharmacokinetics rather than a single property. [12]

BBB permeability should therefore be assessed as an integrated property during CNS degrader development. Computational prediction can be combined with in vitro BBB models and in vivo brain-exposure studies, including brain-to-plasma ratios, unbound brain concentrations and evidence of target degradation. No universal structural strategy has yet emerged for BBB-permeable PROTACs, highlighting the need to integrate molecular design, transporter effects, pharmacokinetics and delivery approaches. [12]

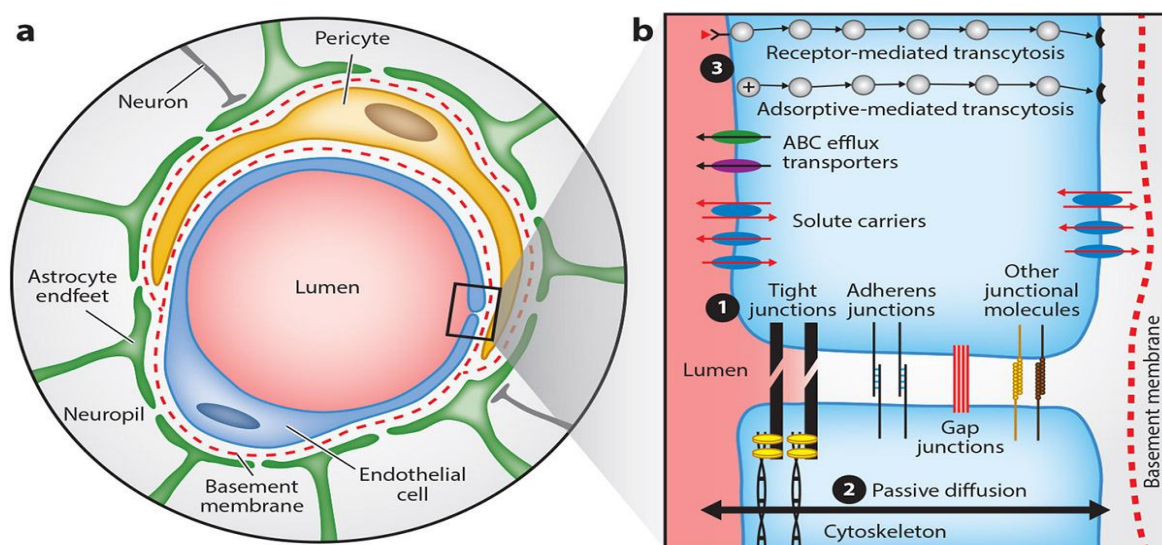


Figure 1: Schematic representation of the BBB structure and major pathways involved in transport across the BBB. Adapted from Wu et al.(2023).[13]

Physicochemical Determinants of CNS Penetration

Successful CNS drug development depends on a balance of physicochemical properties rather than a single parameter. Molecular size, lipophilicity, polarity, hydrogen bonding, ionization and flexibility collectively affect membrane permeability, transporter interactions and brain distribution. This balance is particularly important for targeted protein degraders because their structures may extend beyond the chemical space of conventional CNS drugs. [14], [15]

Molecular Size and Lipophilicity

Molecular weight influences passive membrane diffusion, with increasing size generally reducing BBB permeability. Lipophilicity affects membrane partitioning, but excessive lipophilicity can increase nonspecific binding, reduce solubility and cause metabolic or safety liabilities. For heterobifunctional degraders, the combined size and properties of two ligands and a linker make achieving this balance more challenging.[14], [16]

Polarity and Hydrogen Bonding

Topological polar surface area (TPSA) and hydrogen-bonding properties reflect molecular polarity and can influence membrane diffusion.

High polarity and extensive hydrogen bonding may reduce permeability by increasing the desolvation requirement. These factors are particularly relevant to PROTACs, which may contain numerous heteroatoms and functional groups, although they should be considered alongside other molecular properties rather than as strict exclusion criteria.[14], [17]

Ionization, Flexibility and Intramolecular Hydrogen Bonding

Ionization, commonly described by pKa, affects membrane partitioning and brain exposure through the balance of ionized and un-ionized species at physiological pH. Rotatable bonds and conformational flexibility can also influence molecular behaviour, while intramolecular hydrogen bonding may temporarily mask polar groups and alter effective polarity, potentially supporting membrane permeability.[15], [18]

CNS Multiparameter Optimization

Because no single physicochemical property reliably predicts CNS penetration, multiparameter approaches such as CNS multiparameter optimization (CNS MPO) combine factors including lipophilicity, molecular weight, TPSA, hydrogen-bond donors and basicity-related properties. These tools can aid compound prioritization but are not

definitive predictors of brain exposure. Their use is particularly relevant for protein degraders,

where improving one property may adversely affect another.[16], [19]

Table 2: Source: Compiled and synthesized from the cited literature.

Property	CNS relevance	Concern for PROTACs
Molecular weight	Higher MW generally reduces passive BBB penetration	Many PROTACs are large
Lipophilicity	Influences membrane partitioning	Excessive lipophilicity may increase nonspecific binding
TPSA	Higher polarity can reduce passive diffusion	PROTACs often have high PSA
HBD/HBA	Affect hydrogen bonding and permeability	High H-bonding can reduce BBB penetration
Rotatable bonds	Reflect molecular flexibility	High flexibility may affect permeability and PK
Ionization/pKa	Influences membrane partitioning	Charge can restrict passive diffusion
IMHB	Can temporarily mask polarity	May improve membrane permeability
CNS MPO	Integrates multiple CNS-relevant properties	Useful during CNS optimization

Pharmacokinetic Considerations for CNS Targeted Protein Degraders

Pharmacokinetic evaluation is important for CNS-targeted degraders because systemic exposure does not necessarily indicate adequate drug availability at the neuronal site of action. A degrader must be absorbed, distributed and reach the brain at sufficient concentrations for productive target engagement. Its complex structure may also affect solubility, protein binding, metabolic stability and clearance.[20], [21]

Brain Exposure and Unbound Drug Concentration

Total brain-to-plasma concentration may not reflect the pharmacologically available drug fraction. The unbound brain-to-plasma partition coefficient ($K_{p,uu,brain}$) provides a more informative measure of unbound drug exposure in brain and plasma. Brain exposure should therefore be interpreted with plasma and tissue binding and BBB transporter activity. [22], [23]

Absorption, Distribution and Clearance

Absorption determines systemic availability, while distribution influences access to peripheral

tissues and the CNS. High protein binding, poor solubility or extensive tissue distribution may reduce free drug available for brain entry, while metabolic stability and clearance affect exposure duration. CNS degrader optimization therefore requires a balance between systemic exposure and brain delivery. [20], [21]

PK–PD Relationship and Event-Driven Pharmacology

Unlike conventional inhibitors, degrader concentration and pharmacological effect may decline at different rates. Target degradation can persist after drug levels decrease until new protein is synthesized. Therefore, PK–PD assessment should consider degrader exposure, target engagement, protein degradation and target recovery. This event-driven behaviour can produce sustained effects but complicates dose selection and translational modelling. [20]

CNS Delivery Strategies for Targeted Protein Degraders

The major challenge in CNS-targeted protein degradation is achieving sufficient brain exposure. PROTACs often have high molecular weight, polarity and flexibility that can restrict passive BBB penetration. Delivery strategies

therefore aim to improve degrader permeability or provide alternative transport systems.

Molecular and Formulation-Based Optimization

Degrader structure can be optimized through linker length, polarity, flexibility and the properties of target- and E3-binding ligands. When structural optimization is insufficient, formulation approaches may improve solubility, stability, pharmacokinetics and tissue exposure. Lipid- and polymer-based systems can also encapsulate poorly soluble degraders and support tissue targeting. [24], [25]

Receptor-Mediated and Nanocarrier-Based Delivery

Nanocarriers may promote BBB transport through receptor-mediated transcytosis by targeting receptors such as transferrin or insulin receptors. However, effective delivery requires not only endothelial uptake but also appropriate intracellular trafficking and release of the degrader. [26]

Lipid nanoparticles, polymeric nanoparticles and liposomes provide alternatives to passive BBB penetration. They may protect degraders from premature degradation and enable controlled release, although particle size, composition, surface properties and drug loading require careful optimization because they influence distribution and toxicity. [24], [25]

Intranasal and Nose-to-Brain Delivery

Intranasal administration may provide CNS access through olfactory and trigeminal pathways, reducing dependence on systemic BBB transport. Nanoparticle-based nasal formulations may improve retention and brain targeting, but mucociliary clearance, enzymatic degradation, short residence time and nasal toxicity remain limitations. [27], [28]

For CNS degraders, intranasal delivery is attractive for molecules with poor systemic brain exposure. However, evidence for clinically effective intranasal PROTAC delivery remains

limited, making it an emerging rather than established approach. [24], [29]

Exosome-Based Delivery

Exosomes and other extracellular vesicles are being explored as CNS delivery carriers because they can transport molecular cargo across biological barriers and may be engineered for tissue targeting. Their application to TPD could improve delivery of degraders with unfavourable physicochemical properties, although manufacturing, cargo loading, characterization and biological variability remain challenges. [30]

Integrated Delivery Strategy

No single delivery method currently suits all CNS degraders. Development therefore requires integration of degrader optimization, formulation, BBB transport, brain exposure and intracellular target engagement rather than treating molecular design and delivery separately. [24], [25]

Overall, CNS degrader development requires a balance between degradation potency, brain penetration, pharmacokinetic stability and selective intracellular delivery.

In-silico Evaluation of CNS Targeted Protein Degraders

In-silico methods can support the early design and screening of targeted protein degraders. Unlike conventional docking, degrader modelling must consider interactions among the target, degrader and E3 ligase. Computational analysis can therefore help prioritize promising structures before extensive experimental testing. [31], [32]

Target and E3 Ligase Selection

The process begins with selection of a disease-relevant target and an E3 ligase with suitable expression in the desired CNS region. Experimental or reliable predicted structures can be used to evaluate binding sites and select appropriate ligands or warheads. For CNS applications, E3-ligase distribution is particularly important because the selected

ligase must be available in relevant brain cells. [31]

Ternary Complex Modelling and Molecular Docking

Because a PROTAC must engage both the target and E3 ligase, ternary-complex modelling provides more information than analysing individual interactions alone. Docking and structural modelling can predict possible ternary arrangements and assess whether the degrader positions both proteins appropriately for ubiquitination. [31], [33]

Linker and Molecular Dynamics Analysis

The linker influences PROTAC flexibility and the spatial arrangement of the ternary complex. Molecular dynamics (MD) simulations can therefore help assess its stability and conformational behaviour over time. [33], [34]

CNS Permeability and ADMET Prediction

For CNS degraders, structural modelling should be combined with physicochemical and ADMET prediction. Molecular weight, lipophilicity, polarity, hydrogen bonding, ionization and flexibility can be assessed alongside predicted BBB permeability. Computational and machine-learning models can support early screening, but their predictions require experimental confirmation because BBB transport also involves uptake and efflux mechanisms. [35], [36]

Integrated In-silico Workflow

A practical computational workflow can therefore be summarized as:

Target selection → E3 ligase selection → warhead selection → linker design → ternary complex modelling → docking → molecular dynamics → physicochemical properties → BBB permeability → ADMET prediction → experimental validation.

This integrated approach can prioritize promising CNS degrader candidates and reduce unnecessary synthesis and testing. However, computational predictions remain prioritization tools and cannot by themselves establish

degradation or therapeutic efficacy. [31], [32], [35]

Current Evidence of CNS-Targeted Protein Degraders

Although CNS-targeted protein degradation remains largely preclinical, studies have shown selective reduction of neurodegenerative disease-associated proteins, particularly tau and α -synuclein, which are challenging targets for conventional approaches. [37]

Tau Degradation

Tau is an important target in Alzheimer's disease and other tauopathies. An early peptide PROTAC recruited the Keap1–Cul3 E3 ligase to promote tau ubiquitination and proteasome-dependent reduction, demonstrating the potential of alternative E3 ligases beyond CRBN and VHL.[38]

Later studies reported dual PROTACs capable of reducing α -synuclein aggregates and total tau, suggesting that TPD may simultaneously address multiple pathological proteins in neurodegenerative disease models. [39]

α -Synuclein Degradation

α -Synuclein is another major target, particularly in Parkinson's disease. Arginine-based PROTACs recruiting UBR1 promoted degradation of wild-type and mutant α -synuclein and reduced aggregates and associated toxicity in mammalian cells and a *C. elegans* model. [40]

Alzheimer's Disease-Related Targets

Upstream targets have also been explored. A DAPK1-directed PROTAC reduced DAPK1 in primary cortical neurons and was associated with decreased amyloid- β production and tau hyperphosphorylation, suggesting broader effects through upstream target degradation.[41]

Present Status and Translational Gap

Overall, these studies provide proof of concept for degrading several CNS disease-associated proteins, but evidence remains largely cellular or animal-based. BBB penetration, brain-region exposure, E3-ligase distribution, long-term

safety and adequate degradation in human neurons remain important translational questions. [37], [42]

Table 3: Source: Compiled and Synthesized from the cited primary studies.

Target	Disease relevance	Degrader approach	Key finding	Development stage
Tau	Alzheimer's disease	PROTAC/degrader	Tau reduction/degradation demonstrated	Preclinical
α -synuclein	Parkinson's disease	PROTAC-based approaches	Reduction of pathological α -synuclein demonstrated	Preclinical
Tau + α -synuclein	Neurodegeneration	Dual PROTAC	Simultaneous targeting investigated	Preclinical
DAPK1	Neurodegeneration	PROTAC	Target degradation investigated	Preclinical

Challenges and Future Directions

Despite the potential of targeted protein degradation in CNS drug discovery, clinical translation remains limited by challenges in brain delivery, degrader design, E3-ligase selection, selectivity and experimental-to-human translation.[42], [43]

Limited BBB Penetration and Drug-like Properties

The size, flexibility and polarity of many PROTACs can restrict BBB penetration and affect solubility, absorption and oral bioavailability. Delivery and formulation strategies may help, but achieving adequate and reproducible brain exposure remains difficult.[43]

Limited E3 Ligase Repertoire in the CNS

Most advanced degraders use a limited number of E3 ligases, particularly CRBN and VHL. Their variable expression across brain regions and cell types may affect degradation efficiency, highlighting the need for CNS-enriched or cell-specific E3 ligases.[43], [44]

Selectivity and Safety

Unintended protein degradation is another concern, particularly with molecular glues and CRBN-recruiting degraders that may induce

neosubstrate degradation. Proteomic and functional studies are therefore important for identifying off-target effects.[44]

Need for Better Translational Models

Cell-based assays demonstrate target degradation but cannot fully reproduce the BBB, neuronal environment and regional differences of the human brain. Future development should integrate computational prediction, BBB models, human neuronal systems, pharmacokinetics and appropriate animal models. [42], [45]

Future Perspective

Future CNS degraders may focus on smaller, brain-compatible structures, CNS-selective E3 ligases, improved molecular-glue discovery and targeted delivery. Computational modelling, structural biology and quantitative proteomics may further support degrader optimization and ternary-complex prediction. [43], [44]

Conclusion

TPD provides an alternative CNS strategy by removing disease-associated proteins rather than simply inhibiting their activity. PROTACs and molecular glues have shown preclinical activity against neurodegeneration-related targets, but therapeutic translation depends strongly on

adequate brain exposure and intracellular target degradation.[46]

Key challenges include degrader physicochemical properties, limited BBB penetration, variable E3-ligase expression and pharmacokinetic behaviour. Advances in computational design, CNS-compatible structures, targeted delivery and brain-enriched E3 ligases may help address these limitations. [46]

Overall, successful CNS protein degradation will require coordinated optimization of degrader design, BBB permeability, pharmacokinetics, delivery and target engagement, followed by validation in relevant cellular and animal models before clinical development.

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