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Targeting PICK1 in Drug Discovery: From PDZ Inhibition to Next-Generation BAR and Bivalent Modalities

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Plain Language Summary

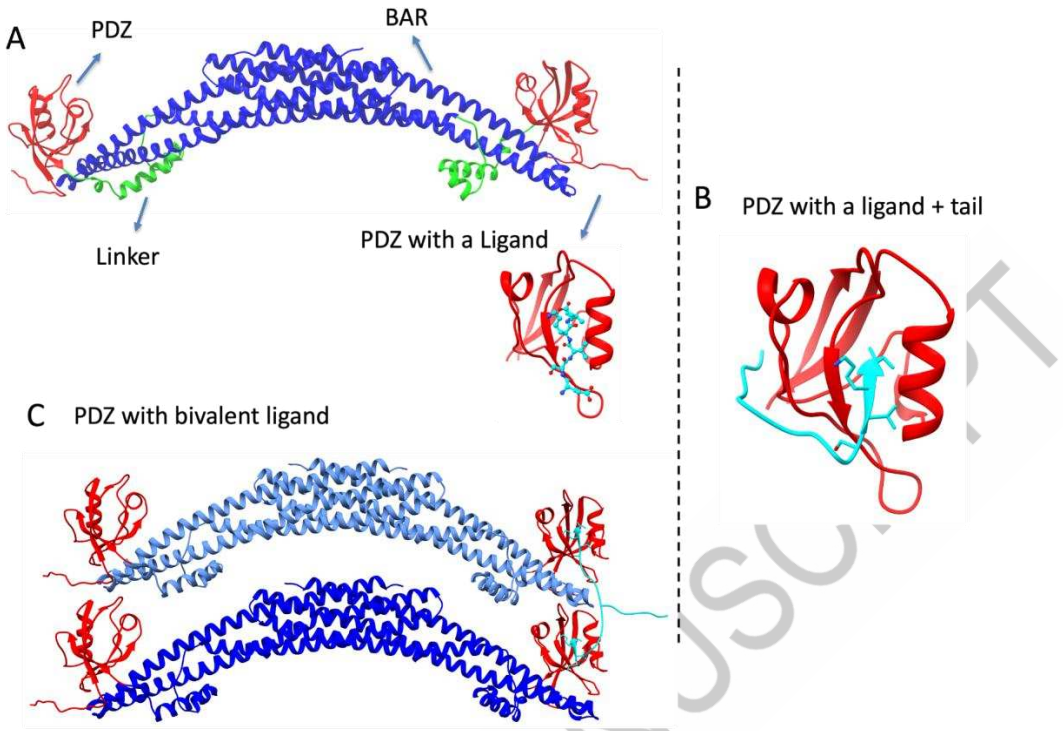
PICK1 is a protein responsible for communication within cells, to guide the positions of other proteins at the necessary time and place. When PICK1 malfunctions, studies have shown it leads to a variety of health problems such as obesity, addiction, and chronic pain. Previous groups have targeted PICK1 with the target being a specific portion of the protein, the PDZ domain, which is responsible for binding other proteins. While this has showed early success, another region of PICK1, the BAR domain, has remained understudied for treating the health issues associated with a malfunctioning PICK1. Artificial Intelligence advances in protein design have made it achievable to design a drug to target both the PDZ and BAR domains simultaneously. This bivalent drug would decrease the possibility of binding to other proteins in the body and enhance the controllability of PICK1's functions.

1. Introduction

Protein Interacting with C-Kinase 1 (PICK1) is a membrane scaffolding protein recognized for its binding to protein kinase C α (PKCα) and its essential role in synaptic plasticity [1–4]. PICK1 is the only known protein that contains both a PDZ (PSD95/Disc-Large/ZO-1) domain and a membrane-binding BAR (Bin/amphiphysin/Rvs) domain, which are connected by a flexible linker region, and it functions as a homodimer. The PDZ domain is believed to interact not only with cell surface receptors but also to facilitate PICK1's interaction with the lipid membrane. In contrast, the BAR domains sense and regulate the curvature of the cell membrane. This regulation allows the PDZ domains to orient themselves toward the C-termini of binding proteins, thereby influencing receptor trafficking. Dysregulation of PICK1's function has been linked to several neurological disorders, including Alzheimer's disease, chronic pain, substance use disorder, and Parkinson's disease [5–8]. Prior Small-angle X-ray scattering (SAXS) studies of PICK1 by Madsen and Dominguez have provided foundational insight into PICK1's structural organization, revealing how the PDZ moves relative to the BAR dimer and establishing a wealth of information regarding membrane engagement and ligand binding accessibility of PICK1 [9,10]. PICK1, as a scaffold protein, carries out its biological function through protein-protein interactions and is traditionally considered an "undruggable" target due to the lack of a well-defined binding pocket for small molecules.

2. Current Progress

One unique characteristic of scaffold proteins, such as PICK1, is that they contain modular domains, such as PDZ and BAR domains (Figure 1A). In particular, the PDZ protein family is a large group that has been studied for decades. Therefore, the PDZ domain has remained an intriguing and feasible therapeutic target due to the availability of high-resolution structural data and its well-defined, conserved C-terminal receptor binding site. This structural information enables researchers to rationally design peptides and small molecules with higher affinity than the natural binders of the PDZ domain. Early work established a structural understanding of how the PDZ domain binds the C-terminal motifs of its natural binders, such as GluR2. Prior studies have shown that PICK1 PDZ preferentially engages Class II ligands with the consensus motif X-ϕ-X-ϕ. Certain Class I ligands, such as PKCα, can also bind, but these interactions rely on additional upstream elements outside the canonical PDZ binding groove to achieve low micromolar affinity.



Marcotte and collaborators initially identified a small molecule, BIO124, which demonstrated that disruption of PDZ interactions with natural binding partners could modulate AMPA receptor activity and trafficking [11]. Madsen and collaborators have pioneered the development of high-affinity PICK1 PDZ inhibitors and used them to demonstrate therapeutic potential across several disease areas, most prominently chronic and neuropathic pain, substance-related behaviors, and metabolic disease models [6,12]. They subsequently developed both monovalent and bivalent peptides derived from the natural binding fragment of the PICK1 PDZ domain, demonstrating not only high binding affinity but also high specificity, as depicted in Figures 1B and 1C. PICK1 PDZ inhibitors with CNS access, such as Tat-P4-$(C5)_2$, have been shown to cross the blood–brain barrier and reduce drug-seeking (for example, cocaine), illustrating that interference with PICK1–receptor PDZ interactions can modify maladaptive glutamatergic plasticity relevant to addiction and, by extension, opioid use disorder mechanisms [12]. Additionally, PICK1 inhibition has been shown to induce weight loss and reduce fat obesity in mice, expanding its therapeutic relevance [13]. In inflammatory and neuropathic pain models, the peripherally restricted bivalent peptide inhibitor mPD5, developed by the Copenhagen group, robustly alleviates both ongoing and evoked hypersensitivity and improves pain-related anxiety and depression-like behaviors without obvious central side effects. These findings highlight PICK1 PDZ blockade as a promising non-opioid strategy for the treatment of chronic pain and diabetic neuropathy which offers no effect on acute nociception as seen in local analgesics [14].

Beyond the nervous system, genetic and functional studies from the same research network have established that PICK1 is essential for insulin granule biogenesis and β-cell function, and that global PICK1 deficiency or modulation alters glucose tolerance in obesity and diabetes models [15,16].

In contrast, the PICK1 BAR domain is known to be responsible for membrane binding, sensing/generating lipid curvature, and Ca2+ regulation [17]. Madsen et al. showed that the PDZ domain and a short helical segment of the linker region regulate BAR domain clustering on recycling endosomes [3]. A subsequent molecular dynamics simulation revealed that the PDZ domain preferred to bind close to tip region of the BAR dimer, and also suggested that the interdomain dynamics is driven by electrostatic and hydrophobic forces [18-19]. Though computer simulations have been used to probe the mechanical properties of the BAR domains, the lack of knowledge on the high-resolution experimentally determined structure of the BAR domain, the sequence of events leading to autoinhibition, and the binding partner dependency limits the in-depth understanding of the biological functions of PICK1 BAR domains [20]. Unlike the PICK1 PDZ domain, which has multiple inhibitors, there are several potential druggable sites in BAR domains, such as the Ca2+ binding region, amphipathic helices, and heteromeric contact surfaces with ICA69/ICA1L, none of these sites have been systematically scanned for small molecules and peptidomimetic binding [21]. It is clear that the knowledge on how BAR domains are activated in biological systems is needed. Moreover, it is necessary to develop or identify a BAR-selective probe so that it can help us potentially understand how BAR participates in synaptic plasticity and possibly reveal the sequence of events tied to such biological processes. This importance suggests that the BAR domain represents not only an unexplored yet potentially powerful therapeutic target for modulating PICK1 activity but also advances our understanding of the biological role of the PICK1 BAR domains.

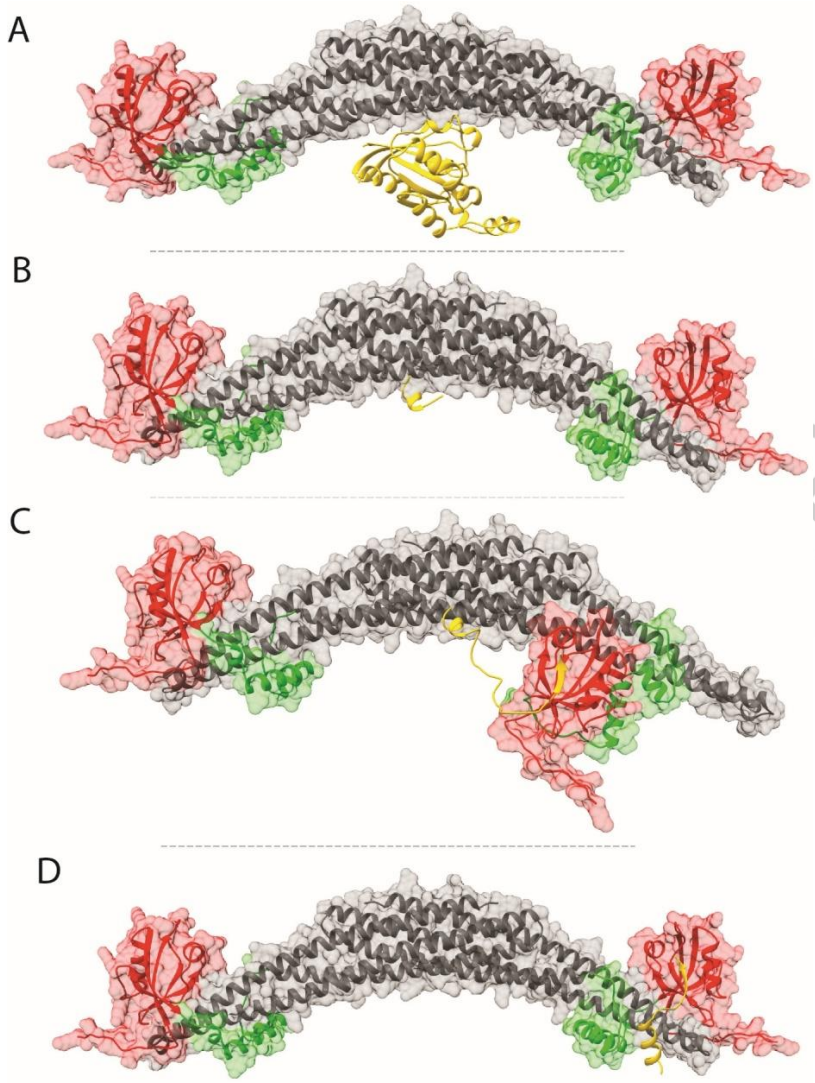
PICK1, as a potential drug target, is not expected to produce many of the sedative, excitability, or addictive side effects, as PICK1 knockout and pharmacological inhibition preserve normal locomotion and behavior in mice. However, preclinical data did indicate several potential off-target risks and warrant careful evaluation [6]. These include a susceptibility to absence-like seizure under specific conditions, possible subtle effects on synaptic plasticity and memory, and a theoretical link to neuropsychiatric disease that is weakly supported by human genetics. In addition, due to its role in vesicle trafficking, it could associate with male infertility, growth retardation, and impaired glucose homeostasis. Because its expression has context-dependent

roles in cancer progression and TGFβ signaling, PICK1 inhibition may have effects on tumor biology.

3. Expert opinion

Prior success in targeting PICK1 based on the assumption that targeting PDZ domain in isolation can break the biological pathway of PICK1 ignoring the dynamics of the whole PICK1 protein which also raises concerns, including limited selectivity among PDZ-containing proteins and the inability to modulate PICK1's functions that are driven by the BAR domain. The rapid advancement of AI-driven methods for protein modeling and engineering has opened new possibilities for rational ligand design. These developments enable extensive exploration of ligand accessibility for protein targets such as PICK1. Such innovative approaches extend beyond traditional PDZ domain targeting and allow for the consideration of dual-domain binders, in which the previously unexplored BAR domain can be targeted to modulate PICK1's function. This strategy offers a means to fine-tune both ligand binding affinity and specificity. Recent computational advances in computational tools, including BindCraft, and Boltz-2, have revealed the feasibility of dual-targeting the PDZ and BAR domains simultaneously [22,23]. Previous work using AfDesign showed that AI-driven tools can effectively serve as high-throughput design methods for generating novel PDZ binders, distinct from the native binding pattern of the PICK1 PDZ domain BindCraft has further demonstrated improved accuracy over its predecessor, AfDesign, for this specific task [24].

As previously reported in earlier experimental studies of Arfaptin (PDB ID: 1I4D), a homologue of the PICK1 BAR domain, the central region of the BAR dimer is capable of binding other proteins (Figure 2A) [25]. Moreover, Madsen et al. have previously suggested that both the PDZ domain and the helical region within the PICK1 linker, directly regulate membrane binding and curvature sensing, thereby modulating how the BAR dimer engages curved membranes [26]. These findings highlight the opportunity to explore a peptide that has the potential to bind to the PDZ domain at its C-terminal and to the BAR domain at its N-terminal. Such binding may occur either at the center of the BAR dimer (as shown in Figure 2B/2C) or at the site where the linker helical region associates with the BAR domain (as illustrated in Figure 2D).



It is known that peptides derived solely from natural amino acids often lack the necessary stability for medical applications, as they can be rapidly degraded. Another option is utilizing synthetic compounds, such as peptidomimetics (N-acylated-N-aminoethyl amino acids/AApeptides, and so on), which can replicate the binding interface of natural amino acid-based ligands, offer a strategy for targeting PICK1 with both high specificity and affinity while maintaining stability in the human body [27,28]. Recent AApeptide studies already illustrate how pharmacokinetic optimization, delivery strategies, and chemical “fixes” can bridge target engagement and therapeutic development [29–31]. These examples underscore that cyclic restraints, peptidomimetic backbones, and targeted chemical modifications are viable and already validated strategies to address PK and delivery challenges for AApeptide-based therapeutics.

Targeting PDZ and BAR domains with a bivalent construct relies on previously reported predicted PICK1 structure ensembles [19]. As computational predictions carry less certainty than experimental work, integrated computational and experimental approaches will guide method development toward critical areas of need while simultaneously testing and refining those methods through feedback. Taking advantage of advanced AI-driven techniques will not only produce designed peptide candidates but also provide screening of all possible druggable sites on PICK1. These computational tools can address both the development of small-molecule probes/drugs and the binding surface challenges that we are currently facing. The specific molecules designed from these tools can provide a starting point to synthesize, evaluate binding affinity, carry out structural validation, and assess membrane permeability, forming a robust design-build-test-learn cycle. Upon reaching nano- or ideally picomolar binding affinity and selectivity, the cycle can be applied to PICK1 PDZ and BAR domains separately as well as target PICK1 dimers as a whole. Success in targeting a single PICK1 modular domain is a milestone and will lay the foundation to develop bivalent constructs. The prior experimental work has laid out the experimental protocol that can be used to validate the computationally designed binders targeting solely the BAR domains or both PDZ and BAR domains, focusing on tracing BAR- dependent clustering on recycling endosomes [26].

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Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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A reviewer on this manuscript has disclosed they have several pending patent applications for PICK1 inhibitors and are a cofounder of Zyneyro, who hold the license to develop these inhibitors toward the clinic for chronic pain conditions. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

AI usage statement

Claude AI, Gemini, and Microsoft Copilot were used for generating synonyms of words and phrases that were originally self-written.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

[1] Staudinger J, Zhou J, Burgess R, et al. PICK1: a perinuclear binding protein and substrate for protein kinase C isolated by the yeast two-hybrid system. J Cell Biol. 1995;128(3):263–271.

[2] Hanley JG, Henley JM. PICK1 is a calcium-sensor for NMDA-induced AMPA receptor trafficking. EMBO J. 2005;24(18):3266–3278.

[3] Madsen KL, Eriksen J, Milan-Lobo L, et al. Membrane Localization is Critical for Activation of the PICK1 BAR Domain. Traffic Cph Den. 2008;9(8):1327–1343.

[4] Xia J, Zhang X, Staudinger J, et al. Clustering of AMPA receptors by the synaptic PDZ domain-containing protein PICK1. Neuron. 1999;22(1):179–187.

[5] Xu L, Chen Y, Shen T, et al. Genetic Analysis of PICK1 Gene in Alzheimer's Disease: A Study for Finding a New Gene Target. Front Neurol. 2019;9:1169.

[6] Sørensen AT, Rombach J, Gether U, et al. The Scaffold Protein PICK1 as a Target in Chronic Pain. Cells. 2022;11(8):1255.
** Discussed extensively regarding potential risks associated with targeting PICK1

[7] Tajbakhsh A, Alimardani M, Asghari M, et al. Association of PICK1 and BDNF variations with increased risk of methamphetamine dependence among Iranian population: a case–control study. BMC Med Genomics. 2021;14(1):27.

[8] He J, Xia M, Yeung PKK, et al. PICK1 inhibits the E3 ubiquitin ligase activity of Parkin and reduces its neuronal protective effect. Proc Natl Acad Sci [Internet]. 2018 [cited 2025 Nov 25];115(30).

[9] Boczkowska M, Rebowski G, Dominguez R. The Challenges of Polydisperse SAXS Data Analysis: Two SAXS Studies of PICK1 Produce Different Structural Models. Structure. 2015;23(11):1967–1968.

[10] Karlsen ML, Thorsen TS, Johner N, et al. Structure of Dimeric and Tetrameric Complexes of the BAR Domain Protein PICK1 Determined by Small-Angle X-Ray Scattering. Structure. 2015;23(7):1258–1270.

[11] Marcotte DJ, Hus J, Banos CC, et al. Lock and chop: A novel method for the generation of a PICK1 PDZ domain and piperidine-based inhibitor co-crystal structure. Protein Sci. 2018;27(3):672–680.

* First reported small molecule targets PICK1 PDZ domain

[12] Christensen NR, De Luca M, Lever MB, et al. A high-affinity, bivalent PDZ domain inhibitor complexes PICK 1 to alleviate neuropathic pain. EMBO Mol Med. 2020;12(6):e11248.

* First bivalent PDZ inhibitor was reported and subsequently evaluated using animal models.

[13] Fadahunsi N, Petersen J, Metz S, et al. Targeting postsynaptic glutamate receptor scaffolding proteins PSD-95 and PICK1 for obesity treatment. Sci Adv. 2024;10(9):eadg2636.

[14] Jensen KL, Christensen NR, Goddard CM, et al. Peripherally restricted PICK1 inhibitor mPD5 ameliorates pain behaviors in murine inflammatory and neuropathic pain models. JCI Insight. 2024;9(20):e170976.

[15] Andersen RC, Schmidt JH, Rombach J, et al. Coding variants identified in patients with diabetes alter PICK1 BAR domain function in insulin granule biogenesis. J Clin Invest. 2022;132(5):e144904.

[16] Li J, Mao Z, Huang J, et al. PICK1 is essential for insulin production and the maintenance of glucose homeostasis. Heldin C-H, editor. Mol Biol Cell. 2018;29(5):587–596.

[17] Stan GF, Shoemark DK, Alibhai D, et al. Ca2+ Regulates Dimerization of the BAR Domain Protein PICK1 and Consequent Membrane Curvature. Front Mol Neurosci. 2022;15:893739.

[18] He Y, Liwo A, Weinstein H, et al. PDZ binding to the BAR domain of PICK1 is elucidated by coarse-grained molecular dynamics. J Mol Biol. 2011;405(1):298–314.

[19] Stevens AO, He Y. Residue-Level Contact Reveals Modular Domain Interactions of PICK1 Are Driven by Both Electrostatic and Hydrophobic Forces. Front Mol Biosci [Internet]. 2021 [cited 2026 Jan 22];7.

[20] Song S, Li T, Stevens AO, et al. Investigating the Mechanical Properties and Flexibility of N-BAR Domains in PICK1 by Molecular Dynamics Simulations. Curr Protein Pept Sci. 24(10):865–877.

[21] Cao M, Xu J, Shen C, et al. PICK1–ICA69 Heteromeric BAR Domain Complex Regulates Synaptic Targeting and Surface Expression of AMPA Receptors. J Neurosci. 2007;27(47):12945–12956.

[22] Passaro S, Corso G, Wohlwend J, et al. Boltz-2: Towards Accurate and Efficient Binding Affinity Prediction [Internet]. bioRxiv; 2025 [cited 2025 Dec 12]. p. 2025.06.14.659707. Available from: https://www.biorxiv.org/content/10.1101/2025.06.14.659707v1.

** effective AI-tool that can handle synthetic compound with reasonable accuracy

[23] Pacesa M, Nickel L, Schellhaas C, et al. One-shot design of functional protein binders with BindCraft. Nature. 2025;646(8084):483–492.

* Can design and screen binding interface of proteins of interests with reasonable accuracy.

[24] Hendrix E, Xia X, Stevens AO, et al. Utilizing AfDesign for Developing a Small Molecule Inhibitor of PICK- 1-PDZ. Curr Protein Pept Sci. 2025;26(10):861–874.

[25] Tarricone C, Xiao B, Justin N, et al. The structural basis of Arfaptin-mediated cross-talk between Rac and Arf signalling pathways. Nature. 2001;411(6834):215–219.

[26] Madsen KL, Eriksen J, Milan-Lobo L, et al. Membrane Localization is Critical for Activation of the PICK1 BAR Domain. Traffic. 2008;9(8):1327–1343.

[27] Niu Y, Hu Y, Li X, et al. γ-AApeptides: design, synthesis and evaluation. New J Chem. 2011;35(3):542.

[28] Shi Y, Teng P, Sang P, et al. γ-AApeptides: Design, Structure, and Applications. Acc Chem Res. 2016;49(3):428–441.

[29] Xue S, Wang X, Wang L, et al. A novel cyclic γ-AApeptide-based long-acting pan-coronavirus fusion inhibitor with potential oral bioavailability by targeting two sites in spike protein. Cell Discov. 2022;8(1):88.

[30] Sang P, Shi Y, Teng P, et al. Antimicrobial AApeptides. Curr Top Med Chem. 2017;17(11):1266–1279.

[31] Xue S, Xu W, Wang L, et al. An HR2-Mimicking Sulfonyl-γ-AApeptide Is a Potent Pan-coronavirus Fusion Inhibitor with Strong Blood–Brain Barrier Permeability, Long Half-Life, and Promising Oral Bioavailability. ACS Cent Sci. 2023;9(5):1046–1058.

Legends

Figure 1 (A) PICK1 dimer composed of the PDZ domain (red), linker (green), and BAR domain (blue). Additionally, an enlarged view of the PDZ domain with its natural ligand (cyan). (B) PDZ domain (red) bound to its natural ligand plus a tail (cyan). (C) Two PDZ domains (red) bound to a bivalent ligand construct with a tail (cyan) in a dimer of dimer PICK1 structure. (NOTE: All panels are for depiction only, and do not reflect the real complex structures.)

Figure 2 (A) PDB ID:1I4D Arfaptin (yellow) bound to PICK1 dimer shown as PDZ domain (red), linker (green), BAR domain (grey). (B) Designed a binder for the BAR domain (yellow). (C) Designed binder targeting the BAR and PDZ domains simultaneously at the concave surface of the BAR domain (yellow). (D) An additional target region of the BAR domain with a designed binder targeting the BAR and PDZ domain simultaneously (yellow).