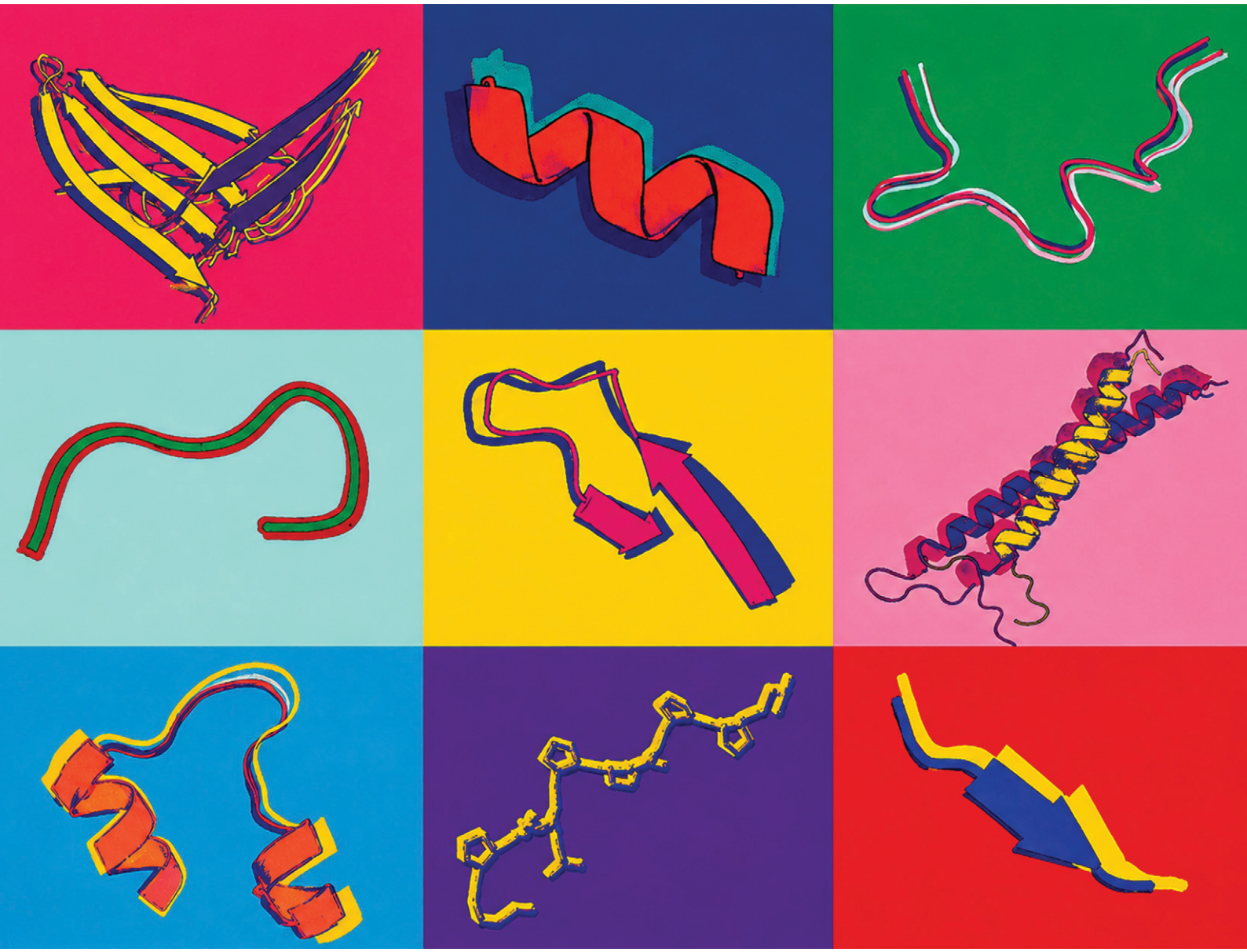
Volume 17
Number 9
September 2026
Pages 3919–4566

RSC Medicinal Chemistry

rsc.li/medchem



ISSN 2632-8682

ROYAL SOCIETY OF CHEMISTRY

REVIEW ARTICLE

Ellie Hyde

Protein–protein interaction inhibitors in the human proteome: lessons from 117 targeted interactions

RSC Medicinal Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

Published on 06 August 2026
Licensed under CC-BY-NC 4.0

Check for updates

Cite this: *RSC Med. Chem.*, 2026, **17**, 3930

Protein–protein interaction inhibitors in the human proteome: lessons from 117 targeted interactions

Ellen E. Hyde and Andrew M. Beekman *

Protein–protein interactions (PPIs) orchestrate cellular function yet remain largely underexploited as therapeutic targets. Although the human interactome is estimated to contain more than 650 000 PPIs, only 117 interactions (~0.02%) have reported inhibitors. Here, we review human PPIs with peptide, peptidomimetic, small-molecule and antibody inhibitors, and classify them according to the dominant secondary structure at the interaction interface. This framework separates PPIs into α-helix-, β-strand- and disordered/loop-mediated interactions, revealing clear links between interface topology and inhibitor discovery strategies. α-Helical interfaces account for most reported inhibitors, whereas β-strand-mediated and dynamic interactions remain comparatively underexplored despite their biological importance. Across structural classes, successful inhibitor discovery has been enabled by structure-guided approaches, including rational peptide design, macrocyclisation, fragment-based screening and peptide-directed ligand design. However, progress remains slow for challenging targets, particularly coiled-coil interactions and intrinsically disordered regions. Emerging technologies, including cryo-electron microscopy and machine learning-guided structure prediction, are rapidly expanding access to these targets. By connecting interface architecture with optimal inhibitor modality and discovery strategy, this review provides a framework for accelerating the development of next-generation PPI therapeutics.

Received 26th June 2026,
Accepted 5th August 2026

DOI: 10.1039/d6md00552g

rsc.li/medchem

School of Chemistry, Pharmacy & Pharmacology, University of East Anglia, Norwich, NR4 7TJ, UK. E-mail: A.Beekman@uea.ac.uk

Protein–protein interactions

Protein–protein interactions (PPIs) are specific, functional contacts between proteins.[1] They underpin all biological functions in living and viral systems, influencing entire



Ellen E. Hyde

Ellie Hyde is a postdoctoral researcher at the University of Bath. She completed a first-class BSc in Pharmacology and Drug Discovery in 2021 from the University of East Anglia. She received her PhD in 2026 from the University of East Anglia under the supervision of Dr Andrew Beekman and Prof. Mark Searcey. Her doctoral research focused on the development of novel peptide and small-molecule inhibitors of protein–protein interactions for anticancer applications, for which she received an award from the British Federation of Women Graduates for the academic excellence of her work.



Andrew M. Beekman

Andrew Beekman is a group leader and Associate Professor of Medicinal Chemistry at the School of Chemistry, Pharmacy & Pharmacology, University of East Anglia. After completing BSc (Hons.) and PhD degrees at the Australian National University, he undertook an Endeavour Research Fellowship at the University of British Columbia, and postdoctoral research at the University of East Anglia. Andrew started as a group leader at the University of East Anglia in 2019, and current research interests include the discovery of protein interaction modulators for proteins, RNA and DNA.

This journal is © The Royal Society of Chemistry 2026

signalling cascades, supporting metabolic activity and gene expression.[1–3]

The diverse biological roles of PPIs result in a remarkable range of interaction types, which can be classified in several ways. Quantitative characterisation of PPIs can be achieved through mathematical analysis of native surface contacts or chemical properties at the interface.[4–6] Experimental quantitative analysis can be achieved by measuring biophysical parameters such as dissociation rates (Kd) and stoichiometry, accomplished by techniques such as surface plasmon resonance (SPR) and isothermal titration calorimetry (ITC) or fluorescence based measurements such as fluorescence polarization and Förster's Resonance Energy Transfer (FRET).[7]

A more binary classification of PPIs is possible by identifying obligate/non-obligate interactions, where proteins can be found as a part of a complex (obligate) or exist independently (non-obligate). Furthermore, non-obligate proteins can produce transient or permanent interactions based on a PPI's stability.[8] Qualitative classification can be collated by protein features, including sequence motifs or individual residue properties, observing binding hotspots by sequence mutagenesis.[9,10] Alternatively, PPIs can also be defined by peptide-domain interactions, as peptide motifs are increasingly being recognised for their contributions towards an interaction.[11,12] The vast complexity of these interactions makes PPIs compelling drug targets due to their high level of specificity and broad application towards a range of disease targets.

Dysregulation of PPIs contributes to the pathogenesis of numerous diseases, particularly well understood in cancer, neurodegeneration and immune diseases.[13–15] PPIs are attractive in drug discovery due to their significant role in biological networks, offering powerful control over disease pathogenesis, instead of targeting a singular protein such as a receptor or enzyme.[16] The clinical translation of PPI inhibitors is accelerating, providing compelling evidence that targets once considered "undruggable" can be successfully modulated therapeutically. A landmark achievement was the approval of Venetoclax in 2016,[17] a BCL-2/BH3 interaction inhibitor discovered through a structure-guided fragment-based drug discovery campaign. Venetoclax demonstrated that small molecules can effectively disrupt high-affinity PPIs and achieve meaningful clinical benefit in patients. Beyond approved drugs, the clinical development pipeline continues to expand, with more than 20 small-molecule PPI inhibitors having entered clinical trials across multiple target classes.[18] The translation of peptide-based approaches has also progressed, exemplified by ALRN-6924, a stapled α-helical mimetic targeting the MDM2/MDMX-p53 interaction, which became the first PPI-targeting stapled peptide to enter clinical trials in 2014.[19] In parallel, antibody therapeutics directed against extracellular PPIs have achieved substantial clinical success, particularly through blockade of immune checkpoint interactions such as PD-1/PD-L1 and CD40/CD40L.[18] Collectively, these clinical milestones establish PPIs as one of the most promising frontiers for the development of next-generation therapeutics. This review provides an overview of the current landscape in developing PPI inhibitors for the human proteome.

Inhibitors of protein–protein interactions

PPIs are notoriously challenging to target due to their large surface area and shallow binding grooves. For instance, although more than 650 000 PPIs are predicted in the human interactome, in 2012, it was predicted that only 0.01% had an inhibitor.[20–24] Despite the increasing popularity of PPI targeting for drug discovery in the following 13 years (Fig. 1A), 85% of the human proteome remains undrugged, highlighting a need to improve our understanding of targeting PPIs.[25,26]

Analyses of PPI inhibition based on buried surface area have shown that larger interfaces are generally more amenable to peptide inhibitors, whereas smaller interfaces are often better suited to small molecules.[21,22,27] Whilst databases exist that categorise small molecule inhibitors of PPIs, these do not consider the contributions of peptide inhibitors towards the field.[28,29] Peptide-based PPI inhibition is typically understood by residue hot-spots, amino acids with significant contribution to the free binding energy of an interaction.[30] The approach taken here looks at the secondary structures that control PPIs, categorising them to better understand the strategies used to design and identify peptides or small molecules inhibitors for particular interaction motifs.

Our analysis of the published literature for protein–protein interaction inhibitors until 2025 found 117 human PPIs (0.02%) with inhibitors (Table 1), doubling the 2012 prediction. Here we provide a review of the human PPI literature, identifying those with peptide or small molecule inhibitors, categorising the types of interactions, and highlighting the techniques used to tackle these challenging targets. This does not include the literature on PPIs between species, from, for example, infection and pathogen invasion.

Many PPIs are driven by short peptide motifs that either adopt defined secondary structures, such as α-helices and

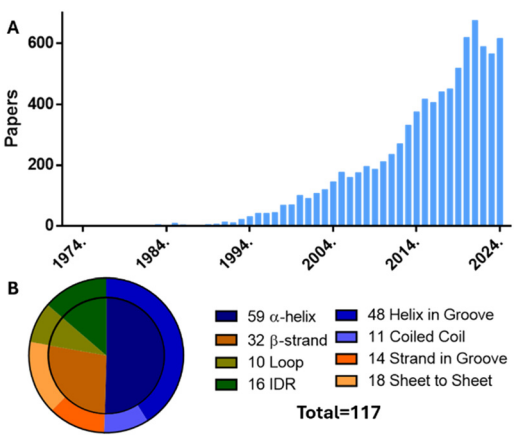


Fig. 1 (A) Publications by year for protein–protein interaction inhibitors from PubMed (B) PPI inhibitors categorised by key secondary structure motif, α-helix (blue), β-strand (orange), loop (yellow), intrinsically disordered region (green).

Table 1 Human protein–protein interactions with reported inhibitors and the year the first inhibitor was reported, categorised by interaction type and inhibitor type[45–154]

Protein-Protein Interactions							
Peptide		**Peptidomimetic**		**Small Molecule**		**mAb**	
Helix-in-groove							
PPI	**Year**	**PPI**	**Year**	**PPI**	**Year**	**PPI**	**Year**
Bcl-2/BH3 domain[45]	1996	Gαq-PLCβ3[46]	2004	β-catenin/BCL9[47,48]	2012	DCN1/UBC12[49]	2017
14–3–3/α-synuclein[50]	1999	Smac/XIAP[51]	2007	Med25/ATF6a[52]	2013	APC/Asef[53]	2017
p53/hDM2[54]	2000	Mcl-1/BH3[55]	2010	HIFα/p300[56]	2013	NF-Y dimer[57]	2019
CBP/p300[58]	2000	AKAP/Calmodulin[59]	2010	EZH2/EED[60]	2013	RbAp48/MTA1[61]	2020
AR/TIF2[62]	2002	ppaF/Sec61[63]	2011	4E-BP/elF4E[64]	2015	PALB2/BRCA2[65]	2020
Cdk5/p25[66]	2002	PP1/RIPPO[67]	2012	TGIF1/SIN3A[68]	2016	SRSF1/SRSF3[69]	2021
Rac1/Tiam1[70]	2004	Collagen/Hsp47[71]	2017	Hsp70/Bim[72]	2021	NPAS3/ARNT[73]	2023
Skp2/CKS1[74]	2005	β-arrestin/AP-2[75]	2017	PRMT5/RioK1[76]	2021	DRP1/MiD49[77]	2023
ATG5/ATG16L[78]	2014	CSF1R/DAPK1[79]	2019	CDK9-cyclin T1[80–82]	2022	RFFL/CFTR[83]	2023
ERCC1/XPF[84]	2015	HSP90/CDC37[85]	2019	CDC42/IQGAP1[86]	2022	NLRP3/NEK7[87]	2024
XRCC4/lig4[88]	2016	NCOA4/FTH1[89]	2021	GIT/PIX[90]	2022	Smad2/3/Smad4[91]	2024
Coiled Coils							
Fos/Jun[92]	2006	EGFR JXT[93]	2014	FOXP3/FOXP[94]	2022	HOP/HSP90[95]	2024
MITF[96]	2012	HSF1[97]	2018	Nrf2/MafG[98]	2023		
Myc/Max[99]	2002	Shroom/Rho[100]	2015	MBD2 /P66a[101]	2019	Beclin 1/ATG14L[102]	2020
Strand-in-Groove							
IgG/FcRn[103]	2006	SENP/SUMO[104]	2004	GKAP/SHANK1-PDZ[105]	2006	PKCe/RACK2[106]	1997
HER2/EGFR[107]	2011	PCSK9/LDLR[108]	2013	APP/Mint2[109]	2021	BRCA2/RAD51[110]	2010
CAD/iCAD[111]	2012	SORT1/PGRN[112]	2013	α-synuclein dimer[113]	2022	BCL6/BCOR[114]	2018
Mad2/Cdc20[115]	2015	Syndecan/Syntenin[116]	2021				
Sheet to Sheet							
CD2/CD58[117]	2002	IL33/ST2[118]	2009	ICOS/ICOS-L[119]	2020	PICK1/GluA[120]	2018
uPAR/uPA[121]	1994	RANKL/RANK[122]	2010	PD-1/PD-L1[123]	2013	CCL5/HNP1[124]	2016
Grb2 SH2 dimer[125]	1996	IL17/IL17A[126]	2013	TNFa trimer[127]	2005	PSD95/nNOS[128]	2009
RUNX1/CBFβ[129]	2015	PRL/CNNM[130]	2008	TG2/FN[131]	2014	RAS/PI3Kγ[132]	2018
Loops							
Keap1/Nrf2[133]	2006	calpain/calpastatin[134]	2009	Menin/MLL[135]	2010	GADPH/δPKC[43]	2016
ERCC1/XPA[136]	2007	MLL1/WDR5[137]	2010	YAP/TEAD[40]	2014		
p62/Keap1[138]	2016	NCS-1/Ric8a[42]	2017	β-TrCP/Nrf2[139]	2022		
Disordered Sequences							
CID/PLCγ1[140]	2018	PLK1/PDB[141]	2003	SALL4/NuRD[142]	2018	Rev1-CT/PolD3[143]	2017
α-synuclein/CHMP2B[144]	2023	PCNA/PIP-box[145]	2012	PARP1/BRCT[146]	2015	SRPK1/SRSF1[69]	2021
p47phox/p22phox[147]	2012	TRIM24/PHD[148]	2015	NHERF1/EBP50[149]	2019	SUV39H1/HP1[150]	2023
BRD9/Histone[151]	2015	DX2/HSP70[152]	2019	ZO-1/CLD[153]	2020	ELF3/MED23[154]	2023

β-strands, or remain intrinsically disordered.[31] Categorisation of human PPIs based on structural characteristics highlights more than 50% of PPIs with reported inhibitors are mediated by α-helical interfaces and over 30% by β-strands. The remaining interactions were categorised as disordered or loop mediated (<20%) (Fig. 1B). Across all structural classes, rationally designed peptides are often the first examples of inhibitors towards PPIs. Equally, screening assays are popular for identifying small molecules inhibitors across all PPI (Table 1).

Categorisation of interactions by secondary structure

Protein–protein interactions can be organised by the presence of interacting α-helix, β-strand or disordered secondary structures (Fig. 2). The most prevalent secondary structure reported at PPI interfaces are α-helices, featured in 62% of multi-protein complexes according to data from the protein data bank (PDB).[32,33] This is likely because much of our understanding of protein interactions comes from crystal structure studies. This may have introduced a disproportionate prevalence of α-helices, as they tend to crystalise more readily due to the stability of their secondary structure.[34,35]

α-Helices most often form a PPI through a helix-in-groove interaction, where the surface of a partner protein forms a hydrophobic pocket (Fig. 2C). Alternatively, they can interact with one another to form coiled coils. These structure-to-structure interactions form a shallow hydrophobic surface, supported by neighbouring ionic interactions between two helices (Fig. 2A).

β-Strands are also capable of forming features in groove (Fig. 2D) and structure to structure interactions (Fig. 2B). Analysis of PDB complexes finds β-strands contribute to 22% of binding interactions.[36] Considering our analysis of PPI

 This journal is © The Royal Society of Chemistry 2026

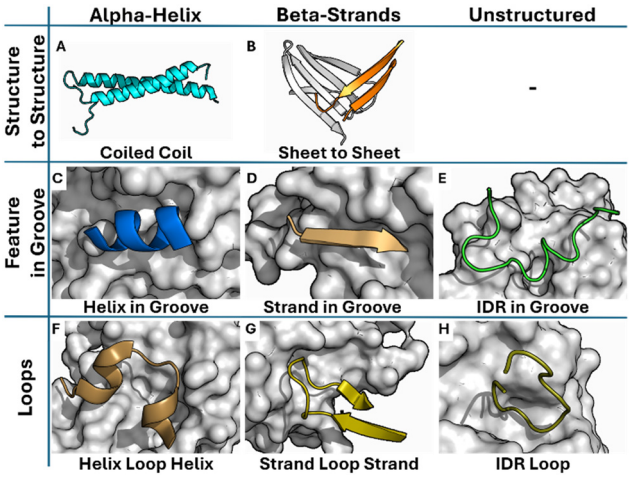


Fig. 2 Examples of protein–protein interactions in proposed categories. (A) Coiled coil interaction MBD2/P66a (PDB: 2L2L). (B) Sheet to sheet interaction ICOS/ICOSL (PDB: 6X4G). (C) Helix-in-groove interaction oestrogen receptor/nuclear coactivator 2 (PDB: 1GWQ). (D) Strand-in-groove interaction GKAP/SHANK (PDB: 7A00). (E) IDR in groove interaction Rev1-CT/PolD3 (PDB: 2N1G). (F) Helix–loop–helix, YAP/TEAD (PDB: 6Q36). (G) Strand-loop-strand PRL/CNNM (PDB: 5 K22). (H) IDR loop ERCC1/XPA (PDB: 2JNW).

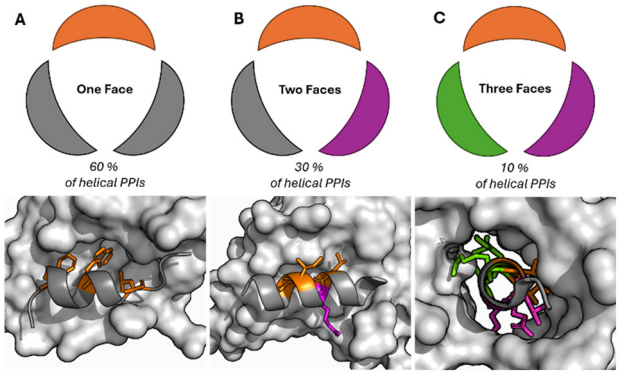


Fig. 3 Percentage of helix-in-groove PPIs with contributions across 1–3 faces of the helix. (A) Examples of one face binding, p53/hdm2 (PDB: 1YCR) (B) two faces, Cdk2/p25 (PDB: 3O0G) (C) three faces, MyoA/MTIP (PDB: 4AOM).

secondary structure (Fig. 1), these statistics appear to correlate with our PPI inhibitor categorisation (50% α-helical, 30% β-strand), highlighting the majority of PPIs known currently rely on α-helix or β-sheet binding into a groove on a partner protein surface.[37]

Dynamic proteins or intrinsically disordered regions (IDRs) lack permanent secondary structures, which can also render IDRs promiscuous in their protein binding partners.[38] However, some IDRs create specific contacts through recognition sequences of amino acids, making them an attractive target (Fig. 2E).[39]

A sub-category of IDRs are loop structures. Loops can be flanked by supporting secondary structures (Fig. 2F–H) but rely on dynamic sequences to bind to the surface of a partner protein. Whilst no literature currently defines the prevalence of these structures, there are increasing reports of inhibitors disrupting these PPIs.[40–43]

Utilising this categorisation, we can review the approaches currently used to target PPIs, highlighting recent advancements and the challenges that remain in PPI drug discovery.

Inhibitors of α-helix mediated interactions

The number of reported PPIs with helices at the interface is more than all other categories combined (Table 1).[32,33,44] Perhaps, the landscape of PPI inhibitors is skewed towards designs for α-helical targets as a result (50% of inhibitors reported). These largely target helix-in-groove interactions, with a smaller collection of α-helix mediated PPI inhibitors reported against coiled coil interactions (9% of inhibitors). This may be due to coiled coil's reliance on shallow knob-in-hole interfaces distributed evenly across the α-helical surface of both protein partners. Multiple approaches for designing peptide and small molecule inhibitors have been described, utilising knowledge of hot-spot residues across small surface areas for both coiled coil and helical binding grooves.[155,156]

Helix-in-groove interactions

Helix-in-groove PPIs can be categorised based on the relative energy contributions of residues across three interfacial domains of an α-helix (Fig. 3).[156] Notably, it is predicted that 60% of α-helical PPIs present hot-spot residues concentrated on a singular face of a helix (Fig. 3A).[33] Peptide inhibitors frequently serve as chemical probes for screening assays or to direct small molecule inhibitor discovery towards a desired interaction site. Alternatively, small molecule inhibitors can be designed to mimic key binding residues of a helical peptide sequence.

Helix-in-groove inhibitor design strategy: rational peptide design

Structural information of a helical sequence can provide valuable information on the location of key binding pockets on a binding surface, and subsequent peptide inhibitor design. An example of this is the helix-in-groove interaction between the N-terminal transactivation domain of p53 and its negative regulators *h*DM2/x, which promotes nuclear export and degradation of p53. The α-helix of p53 engages a deep hydrophobic pocket on the *h*DM2/x *via* a singular face of the helix (Fig. 3A). Structural studies of p53 have revealed that this interaction is driven by three residue hotspots, Phe19, Trp23 and Leu26 along the helix.[157,158] Peptides derived from the native p53 sequence display nanomolar affinity for *h*DM2 in biophysical studies.[159]

Another well characterised example of a helix-in-groove interaction is the helical BH3 domain of Bid, Bim or Noxa binding to pro-apoptotic protein Bcl-2. The conserved BH3 helix occupies four hydrophobic pockets on a singular face of the α-helix with key isoleucine and phenylalanine residues.[160] Utilising the native sequence, high-affinity peptides were

synthesised, forming the basis of competition binding assays to engineer Bcl-2 specific peptides with nanomolar affinity.[161,162]

Helix-in-groove inhibitor design strategy: peptide libraries

Surface display screening techniques or peptide arrays can help researchers screen large combinatorial peptide libraries to achieve greater affinity for a PPI compared to wild-type peptides. Surface display technology combines genetic recombination with affinity selection to screen large varieties of peptide sequences towards a protein target.[163–165] Peptide arrays utilise immobilisation of a large number of peptide sequences on a solid support, offering a high-throughput approach to residue scanning within a peptide to gain understanding of interactions to a PPI interface.[166,167] This has been achieved for the helix-in-groove PPI between Bim/Bcl-xL. This technique has achieved nanomolar potency for the displacement of rationally designed wild-type peptide in fluorescence polarisation assays.[161,162]

Phage display methods have also improved upon the sequence affinity of p53 wild-type peptides, observing two-fold greater affinity for *h*DM2/x proteins. Interestingly, the lead peptides retained the core hotspot residues.[168] Further investigation by residue scanning has highlighted the importance of non-contact residues in stabilising helical conformations in both wild-type and display-derived peptides.[169] Mirror image phage display has also been used to identify D-amino acid sequences with affinity for MDM2, overcoming proteolytic susceptibility of peptides.[170]

Helix-in-groove inhibitor design strategy: helical mimetics

Peptide inhibitors offer a scaffold for the design of small molecule inhibitors, guiding the development of peptidomimetics. Helical mimetic scaffolds have been reported for hot spot functionality across all three faces of helix-in-groove forming interactions. On a singular face of an α-helix several scaffolds have been reported, with molecular modelling studies

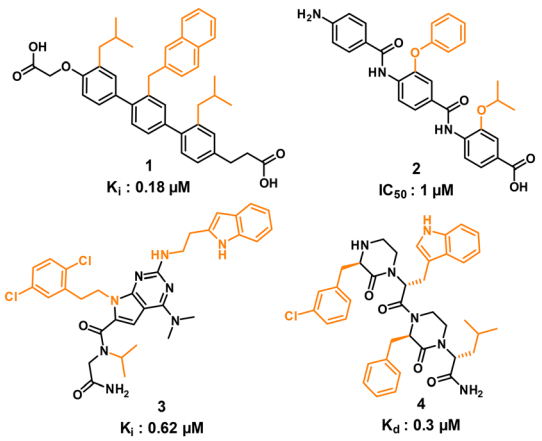


Fig. 4 Helical mimetic scaffolds for inhibition of p53/hDM2 helix-in-groove interaction. (1) Terphenyl scaffold[171] (2) benzamide scaffold[172] (3) pyridyl-pyridone scaffold[173] (4) oxopiperazine scaffold.[174] Side-chain mimetics highlighted in orange.

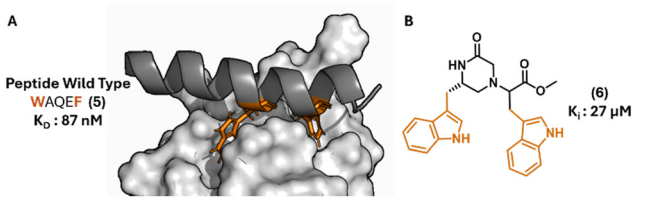


Fig. 5 (A) PEX5/PEX14 (PDB: 2 W84). (B) Oxopiperazine helical mimetic (**6**).[175]

showing good overlap for coverage of the *i*, *i* + 4 and *i* + 7 residues within a helix.[176,177] Inhibitors of p53/hDM2 terphenyl (**1**), benzamide (**2**), pyridyl-pyridone (**3**), and oxopiperazine (**4**) structures have demonstrated nanomolar inhibition for helix-in-groove interactions including p53/*h*DM2 (Fig. 4). Helical mimetic scaffolds have also been utilised to afford inhibitors of Bcl-xL/Bak, Cdc42/Dbs and Hif1α/p300 PPI's.[33,155,178,179]

Oxopiperazine scaffolds have been applied for the inhibition of the PEX5-PEX14 single facing helical interaction (Fig. 5). Peroxin (PEX) proteins are responsible for biogenesis of peroxisomal pathways in trypanosome parasites. PEX5 produces an amphipathic helix on a singular face with key tryptophan and phenylalanine residues across a five-residue sequence (WxxxF) (**5**).[180] The small interaction site makes the PPI an ideal candidate for an oxopiperazine mimetic approach, designing a small molecule inhibitor of the interaction. After a structure based design campaign, a lead compound (**6**) with a K_i of 27 μM was afforded for the PEX5/PEX14 interaction (Fig. 5B).[181] This demonstrates promise for helical mimetics across short surface areas in helix-in-groove interactions without the need for excessive compound screening.

Building on this principle, other helix-in-groove PPIs have been targeted using a scaffold-based approach. Steroid receptors and their coactivators form helix-in-groove PPIs across two faces of the helix on the co-activator protein (Fig. 6). The oestrogen receptor utilises three key hydrophobic points of contact with leucine residues (LxxLL) (**7**) which has been used to design helically constrained peptides and small molecule inhibitors utilising a pyrimidine scaffold (**8**) to reach the three binding pockets across the receptor surface with a K_i of 29 μM for the displacement of a peptide containing the LxxLL motif.[182]

The helical interaction between MTIP and the myosin A tail in *Plasmodium falciparum* is one of the few literature examples of successful PPI inhibitors for interactions across

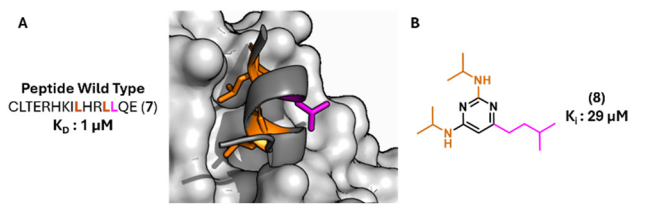


Fig. 6 (A) Helix-in-groove interaction of nuclear coactivator with oestrogen receptor (PDB: 1L2I). (B) Pyrimidine based inhibitor (**8**) designed from the GRIP-1 peptide (**7**) LxxLL motif, highlighted in orange and magenta.[182]

This journal is © The Royal Society of Chemistry 2026

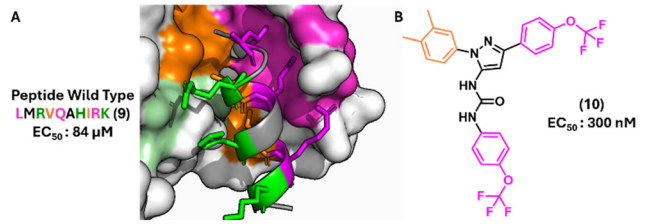


Fig. 7 (A) MyoA peptide binding to MITP protein surface (**9**). Three helical faces highlighted in green, orange and magenta. (PDB: 2AUC) (B) pyrazole-urea compound (**10**) with surface interactions coloured in orange and magenta.[183]

three faces of a helix. Myosin tail interacting protein (MTIP) forms a closed complex around the Myosin A (MyoA) tail helix which stabilises the interaction using eight key charged or hydrophobic residues (Fig. 7).[184] Across a 15-mer peptide sequence (**9**), it was found that a helical peptide based on the MyoA tail could inhibit *P. falciparum* growth with an EC_{50} of 84 μM.[185] Analysis of the hotspot residues of the 15-mer helical peptide led to the identification of a class of pyrazole-urea compounds (**10**) with a lead compound capable of inhibiting parasite growth (EC_{50} of 300 nM). Structural modelling demonstrated the ability of the compound to bind several of the binding pockets found by two of the helical faces of the MyoA peptide (Fig. 7B).[183]

Helix-in-groove inhibitor design strategy: peptide-directed ligand design

An emerging method for the identification of small molecule inhibitors of helix-in-groove interactions is peptide-directed ligand design. By utilising knowledge of hot-spot residues in a peptide sequence, peptide-small molecule hybrids show improved affinity for a target protein in a PPI. This has been achieved for helix-in-groove interactions including cdk2/cyclin A, p53/*h*dm2 and Noxa/Mcl-1.[186–189] Notably, combining *in silico* screening with synthesis achieved a 50% success rate in binding assays towards the p53/*h*dm2 interaction.

A peptide inhibitor of the Noxa/Mcl-1 interaction (Fig. 8A) has been used as a scaffold (**11**) to investigate small molecule fragments active in displacing the wild-type helix-in-groove PPI (Fig. 8D).[187] *Via* peptide-small molecule hybrids (**12–19**), this led to the identification of potent small molecule inhibitors for the interaction (**20–21**).[187,188] This approach provides a more efficient route to small-molecule PPI inhibitors than conventional high-throughput screening.[187,188]

Inhibitors of coiled coil mediated interactions

Coiled coils are made up of α-helices capable of forming helix-to-helix interactions. These form from two or more α-helices winding into a super-helix.[190] Coiled coils benefit from a repeated heptadic motif $(abcdefg)_n$ (Fig. 9). These structures are amphipathic in nature, with hydrophobic amino acids conserved at positions *a* and *d* and polar residues at positions *e* and *g*.[191] On complementary monomers, *a* and *d* positions

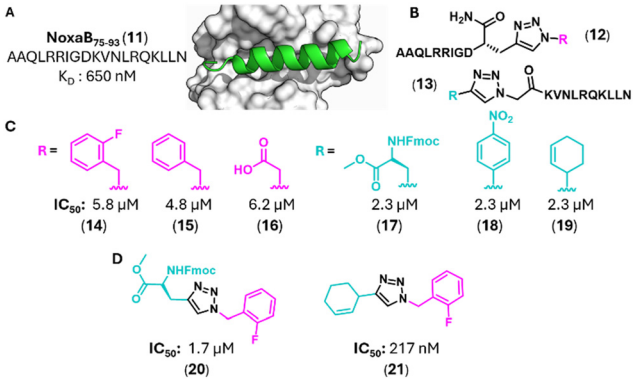


Fig. 8 Peptide directed-ligand design. (A) Noxa/Mcl-1 interaction (PDB: 2NLA) and NoxaB peptide. (B) Triazole linked peptide-small molecule hybrids. (C) Small molecule fragments that compete with NoxaB peptide. (D) Resulting small molecules inhibitors.[187,188]

associate to create a hydrophobic core. Coiled coils can exist naturally as dimers, trimers, or tetramers. Coiled coil assemblies containing three or more helices are often referred to as helical bundles.

Coiled coil inhibitor design strategy: rational peptide design

Coiled coil peptide inhibitors have been discovered through rational sequence design. Using native protein sequences from dimeric coiled coils forming transcription factors such as Myc-Max, Fos/Jun and GCN4 peptides PPI inhibitors have been identified.[92,192,193] Improvement on the linear peptide sequence can be made through incorporation of a hydrocarbon staple across the external face of the helix. This was effectively deployed for an Nrf2-derived 16-mer which inhibited Nrf2/MafG binding (K_d = 337 nM).[98]

Coiled coil inhibitor design strategy: combinatorial libraries

Combinatorial libraries have been used to find peptide inhibitors against the Fos/Jun and microphthalmia associated

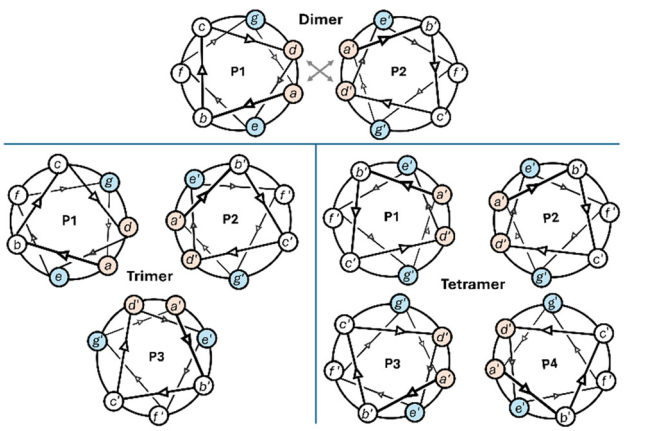


Fig. 9 Helical wheel diagram of residue positions on coiled coil interacting proteins. Hydrophobic positions "a" and "d" (orange), polar positions "e" and "g" (blue).

transcription factor (MTIF) coiled coil interaction.[92,96] Used in combination with protein fragment complementation assays, screening sequence libraries for improved coiled coil interactions achieved lead peptide coiled coil disrupters at low μM concentrations.[92,194]

Coiled coil inhibitor design strategy: *de novo* peptide design

Due to the highly ordered nature of sequences found in coiled coil interactions, it is possible to design *de novo* peptide sequences to inhibit this type of PPI.[195–197] Coiled coil forming peptide sequences are predicted using computational models and experimentally determined using peptide arrays.[195] For example, SYNZIP was used to generate peptides specific to basic leucine zippers (bZIPs) and found that over 80% of peptide designs synthesised could bind to their target protein.[195] However, 40% were also capable of self-association, an added challenge in designing coiled coil forming peptides.[198]

More recently *de novo* peptide design was applied using CCbuilder to form crosslinked helical dimers capable of selectively sequestering Myc and inhibiting PPI formation with Max. Researchers designed *de novo* peptides capable of stable coiled coil formation in complex with Myc with nanomolar affinity, without disrupting the Max homodimer.[199]

Coiled coil inhibitor design strategy: small molecule identification

Small molecule inhibitors of coiled coil interactions are limited. This has largely been due to the shallow binding pockets characteristic of coiled coils.[200] HTS has identified several small molecule inhibitors against the Myc/Max dimer.[99,201,202] Disruption of the interaction may occur through binding into the loop region in the centre of the helix–loop–helix of Myc, rather than directly binding to the Myc α-helix. *In silico* screening has helped improve the hit rate of HTS identification of small molecule inhibitors of the MDB2/p66α coiled coil with two lead compounds demonstrating low micromolar activity (IC_{50} of 1.5–1 μM).[101] Other small molecule inhibitors are reported against larger helical bundle structures, found by HTS methods, perhaps benefitting from a deeper binding groove forming across multiple helices.[100,102] Considering alternative routes to HTS may offer more efficient methods for disruption of this type of PPI by small molecules. The predictable heptadic assembly of coiled coils offers guidance on key residues that could be employed to derive helical mimetic small molecules similar to those derived from helix-in-groove interactions.[203]

Inhibitors of β-strand mediated interactions

A β-strand is a 3–10 amino acid sequence forming a pleated backbone motif through tetrahedral bond formation around the Cα atom.[204] β-sheet structures occur from two or more β-strands connected laterally through hydrogen bond networks to form twisted flat sheets at dihedral angles of 135°/−135°.[205] Most interactions mediated by β-strands can be categorised as a strand or hairpin into a binding groove or a β-sheet interaction with another β-sheet (Fig. 2). Hotspot analysis of β-strand mediated PPIs has found the majority employ residues on faces for hydrogen bonding or side chain interactions with a partner protein, often with uneven and unpredictable distribution.[36]

β-Strand and β-sheet interaction inhibitors

β-Sheets form through three or more connected β-strands, twisted into parallel or anti-parallel pleats to create a large and flat surface area. Designing mimetics for β-strand and β-sheet mediated PPIs presents significant challenges compared to α-helices. In particular, β-strands can be prone to aggregation, driven by interstrand hydrogen bonding networks with adjacent strands. Consequently, mimetics require careful design to minimise self-assembly.[206,207]

β-Strand inhibitor design strategy: rational peptide design modifications

Short peptide sequences can fail to adopt secondary structure. Peptidomimetic strategies such as *N*-substitution of backbone amides can help support β-sheet formation (Fig. 10B). *N*-Methylation to constrain peptide backbones has been used to improve activity of inhibitors towards the small ubiquitin-like modifier (SUMO) interaction with the SUMO interacting motif (SIM) of RanBP2 (Fig. 10A).[208] *N*-Methylation screening of a 13-mer peptide sequence (**21**) of the RanBP2 SIM improved the IC_{50} and K_D two-fold compared to the parent peptide in two of the twelve derivatives synthesised (Fig. 10C).[209]

β-Strand inhibitor design strategy: peptide-directed ligand design

Peptides offer an advantage over small molecules to afford β-strand inhibitors due to their ability to interact over a large flat surface.[210] Information gained from peptide inhibitors of β-sheets can direct efforts to afford small molecule inhibitors (Fig. 11). Peptide-directed ligand design has been applied to the Shank1 PDZ/GKAP PPI identifying peptide-small molecule hybrids with improved activity over the wild-type 6-mer GKAP derived β-strand peptide. Ac-EAQTRL-OH, (**23**) has a K_D of 1 μM determined by fluorescence polarisation against the Shank1 PDZ. Connecting a library of small molecule fragments to truncated 3-mer sequence (**24**) by arylhydrazone bond formation (Fig. 11B), led to the identification of hit compounds with low μM IC_{50} competing with the native peptide (Fig. 11C).[211]

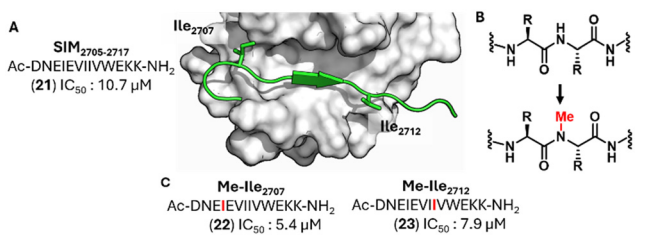


Fig. 10 (A) SIM/SUMO interaction (PDB: 2LAS). (B) *N*-Methylation of the peptide backbones. (C) Hit SIM peptides with *N*-methylated isoleucine residues.[209]

This journal is © The Royal Society of Chemistry 2026

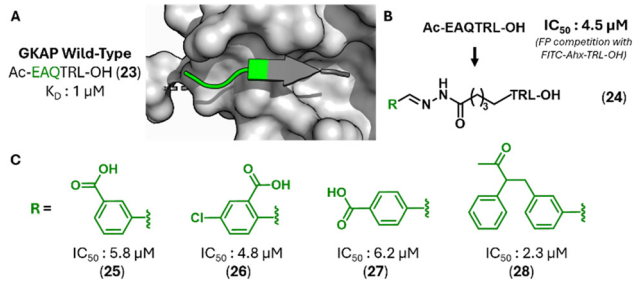


Fig. 11 Peptide-small molecule strategy for GKAP/SHANK1 interaction. (A) GKAP C-terminal peptide (PDB: 1Q3P). (B) Peptide hydrazone structure. (C) Structures of hit compounds with IC_{50} reported by competition fluorescence polarisation.[211]

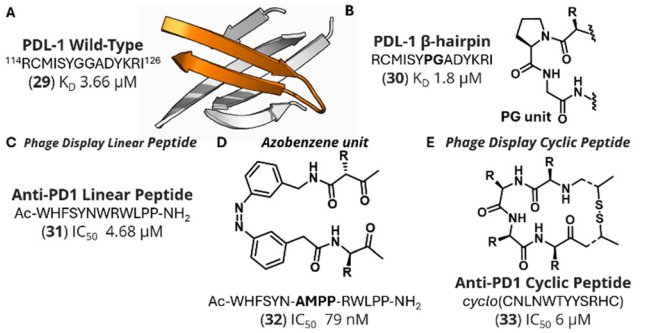


Fig. 12 PD-1/PDL-1 inhibitor strategies. (A) Native PD-L1 derived peptide (orange) interacting with PD-1 (PDB: 4ZQK). (B) Proline-glycine turn unit installed into native PD-L1 peptide.[220] (C) Phage display derived PD-1 binding peptide.[208] (D) Azobenzene unit containing peptide.[209] (E) Cyclic phage display peptide containing disulfide bridge.[217–219]

β-Strand inhibitor design strategy: small molecule identification

Currently reported small molecule inhibitors of β-sheet interactions have been identified through HTS of large compound libraries, achieving remarkably low hit rates around 0.01%.[129,212,213] Characterised by hydrophobic binding interactions, small molecules found this way benefit from extended aromatic ring structures to capture π–π stacking interactions between inhibitors and the target protein.[129,213–216]

In silico library screening has been applied to improve hit rates in conjunction with structure guided approaches to PPI inhibition. Interestingly, applying the same library screen towards a β-strand-in-groove interaction has been shown to produce a lower hit rate compared to an α-helix-in-groove PPI.[31] Recognition of this gap in pharmacophore libraries designed to target β-strand interactions could guide development of tailored scaffold libraries, improving drug discovery toward alternative PPIs.

β-Sheet peptide inhibitor design strategies

Designing inhibitors of β-sheet interactions can be achieved through peptides derived from native sequences of interacting sheets. In this approach cyclic or hairpin peptides sit flat across the β-sheet surface, with every other side chain pointing towards the β-sheet surface, directly mimicking a β-sheet interaction. The PD-1/PD-L1 interaction provides an example where β-hairpin structures have been used to induce turn structures in peptides and small molecules (Fig. 12.[217–219]) Where the native peptide sequence of a hairpin β-sheet of PD-L1 (**29**) has affinity for the PD-1 β-sheet, residue mutation from glycine to proline improved binding affinity 2-fold (**30**). Peptides capable of disrupting the PD-1/PD-L1 PPI have also been found by phage display techniques (Fig. 12C and E). Linear peptides (**31**) were further improved by installing an azobenzene turn unit (**32**) generating a light-activated β-hairpin forming peptide (IC_{50} of 79 nM), with greater activity than the parent peptide (IC_{50} of 4.6 μM).[219]

Macrocyclisation-inducing units can be applied to peptide inhibitors to constrain β-sheet mimetics, such as the ICOS/ICOS-L interaction (Fig. 13A). Employing known key residues involved in the ICOS-L β-sheet, Tyr51, Tyr53 and Gln55, an *in silico* design strategy was used to design a macrocyclic peptide towards the ICOS β-sheet. Introducing Pro-Gly, D-Pro-Gly turn units, disulfide bridge combinations and residue optimisation, led to a 12-mer bicyclic peptide inhibitor (**34**), with an IC_{50} of 22.8 μM by TR-FRET against the ICOS/ICOS-L interaction (Fig. 13B).[221]

Small molecule inhibitors of β-sheets

Small molecules have been found through fragment high-throughput screening against β-sheet mediated PPIs.[222–224] However this approach remains inefficient, with most inhibitors reporting micromolar activity. Even the most potent of small molecule inhibitors are a product of hit-rates below 2%.[225]

Inhibitors of dynamic protein region interactions

PPIs mediated by intrinsically disordered regions (IDR) often lack a defined secondary structure, relying on hotspot residues within a dynamic recognition sequence, or constrained loops between secondary structures that can be reproduced by macrocyclisation. Often disordered PPI structures will occupy a well characterised binding pocket, which can be exploited when

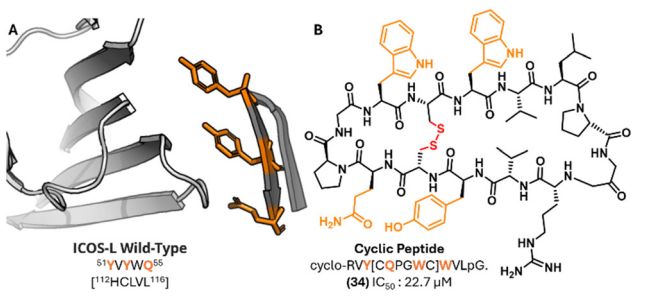


Fig. 13 ICOS/ICOS-L interaction. (A) Interaction of ICOS-L β-strand, key residues highlighted in orange (PDB: 6X4G). (B) Cyclic peptide structure of ICOS-L derived bicyclic peptides proposed key residues highlighted in orange.[221]

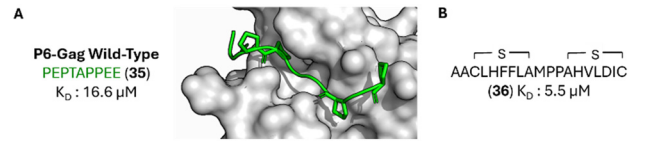


Fig. 14 UEV/p6-Gag interaction. (A) 9-mer p6 proline recognition sequence (green, **35**) (PDB: 3OBU).[226] (B) macrocyclic peptide (**36**).[227]

designing inhibitors. Loops between fixed secondary structures are less flexible that true IDRs, but their flexibility has made inhibitor design challenging. As such, methods to constrain loop structures have been applied to peptide inhibitor design. Reports of inhibitors against dynamic PPIs has increased the most in the last decade (Table 1). Inhibitors are increasingly incorporating structural information from peptide inhibitors to guide small molecule discovery.[140,143,145,146]

IDR inhibitor design strategies: peptide combinatorial libraries

Disordered PPIs forming from recognition sequences can be targeted by native and random peptide sequences (Fig. 14). The HIV-1 Gag p6 protein binds to host Endosomal Sorting Complex Required for Transport (ESCRT-I) Ubiquitin E2 variant (UEV) subunit through a disordered 9-mer sequence (**35**). As the ESCRT protein is highly structured, information about the binding groove of the PPI is well characterised, despite the lack of secondary structure from the p6 binding protein (Fig. 14B).[226]

Whilst small molecules disrupting the UEV-p6 PPI have yet to be reported, peptide modifications have been explored using screening by genetically encoded libraries. Screening of the lanthipeptide library of 10^6 macrocyclic peptides with a bacterial display system identified lead peptide **36**, that demonstrated a 3-fold improvement over the parent peptide in binding to the UEV protein.[227] Interestingly the hit peptide bears no sequence similarity to the wild-type, raising questions as to the mode of PPI inhibition (Fig. 14B).

IDR inhibitor design strategies: peptidomimetics

Peptidomimetics can improve inhibitor activity, using hot-spot residues as an anchoring scaffold to explore the surrounding chemical space. This has been achieved in the IDR PPI between a phosphoprotein recognition sequence to the BRCA1 protein (Fig. 15A).[228] Utilising a small molecule microarray, peptidomimetics were generated (**38**) conserving a key phosphoserine anchoring to the binding pocket (Fig. 15B).[228–230] This led to a 3-fold improvement in IC_{50} against the native phosphopeptide binding sequence (**37**) by retaining the key Trp, pSer and Phe moieties of the native peptide sequence (Fig. 15C).

IDR inhibitor design strategies: small molecule identification

Rational approaches to IDR PPI inhibitors have yielded highly potent small molecule inhibitors. The well-defined binding pocket found in the bromodomain and extra-terminal

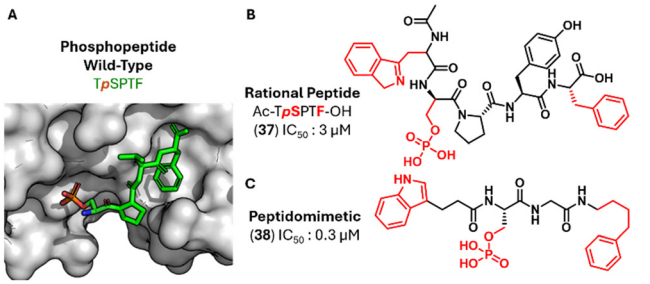


Fig. 15 (A) Phosphopeptide (green) recognition sequence interacting with BRCA1 (PDB: 3K0K). (B) Phosphopeptide derived peptide (**37**), hotspot residues highlighted in red.[228] (C) Lead phosphopeptidomimetic (**38**).[228–230]

domain (BET) family of proteins relies on acetylated lysine (KAc) for recognition of IDR PPIs with histone proteins (Fig. 15A).[232,233] The first examples of bromodomain PPI inhibitors investigated thienodiazepine structures with anti-inflammatory activity. Structure–activity-relationship studies developed a small molecule (**40**) capable of displacing peptide binding to the bromodomain-containing protein 4 (BRD4) (Fig. 16). Modelling small molecules off the key KAc residues achieved nanomolar IC_{50} values in competition against the parent peptide (**39**).[232]

Inhibitors of loop mediated interactions

An emerging target for PPI inhibitors are loop structures at interaction sites, with evidence from the PDB that as many as 50% of protein complexes feature mediation by loops.[234,235] The majority of characterised loop interactions were β-turns (31%) followed by loops between α-helices (11%).[234]

Loop mediated inhibitor design strategies: rational peptide design

Loops present a unique challenge compared to α-helices and β-sheets interactions, as they lack predictable structures to manufacture standard scaffolds across a range of targets.[236] Identification of key hot-spot residues within loops has allowed for the identification of attractive interfaces such as Nrf2/Keap1 and YAP/TEAD.[234]

Macrocyclisation of wild-type peptides can improve peptide affinity in loop mediated PPIs (Fig. 17). For example,

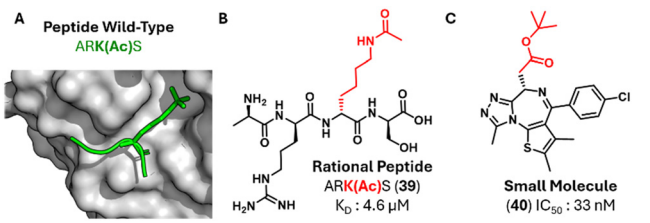


Fig. 16 BRD4/histone interaction. (A) Protein H3K14ac peptide (**39**) (PDB: 3JZG), 4-mer acetylated lysine recognition sequence (green). (B) Acetylated peptide with affinity for BRD4 protein.[231] (C) Small molecule JQ1 (**40**).[232]

This journal is © The Royal Society of Chemistry 2026

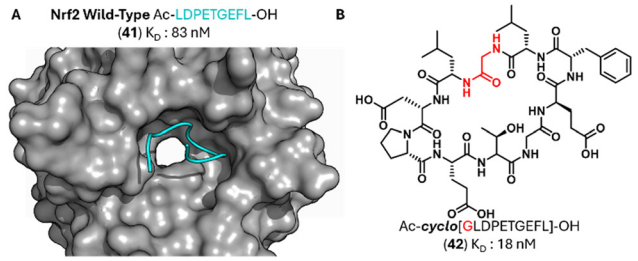


Fig. 17 Nrf2/Keap1 interaction. (A) Nrf2 ETGE loop motif bound to Keap1 (PDB: 2DYH). Linear peptide (**41**) and (B) cyclised Nrf2 derived peptide (**42**).[237]

inhibition of the loop unit of Nrf2 engaging the Keap1 β-propeller has been achieved using a glycine linker for head-to-tail cyclisation of the Nrf2 derived linear LDPETGEFL (**41**) improving the K_D from 86 nM to 18 nM in SPR, demonstrating a 4-fold increase in binding affinity (**42**).[237]

Peptides incorporating non-natural amino acids have achieved potent inhibition of loop mediated interactions, such as the YAP-TEAD helix–loop–helix (Fig. 18A). Investigation by mutation studies has identified hot-spot residues and key positions for installation of turn units.[40] This led to a 15-mer peptide inhibitor (**44**) improving linear peptide inhibition from IC_{50} of 68 μM to 9.2 nM (Fig. 18B).[238]

Loop mediated inhibitor design strategies: small molecule identification

Following similar trajectories to the inhibitors of α-helix and β-strand mediated PPIs, screening assays have identified inhibitors of loop mediated PPIs, achieving similarly low hit rates.[212] However, once a hit compound has been found, SAR studies can achieve greater potency towards a target PPI.

A well-documented example of this is the naphthalene containing small molecules found to inhibit Nrf2/Keap1.[239]

Initially found by HTS against the wild-type peptide, several iterations explored the chemical space occupied in the hydrophobic binding pocket formed by Keap1.[240–244] Fragment-based drug discovery has also been applied

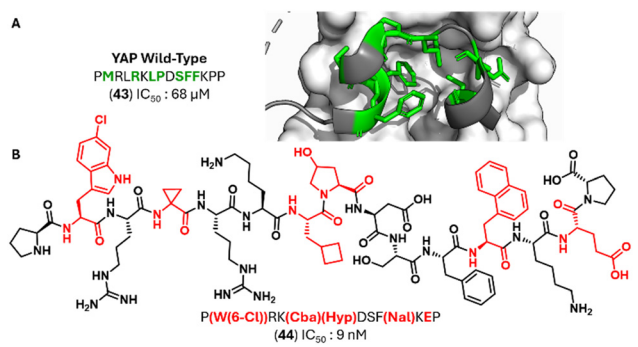


Fig. 18 (A) YAP/TEAD interaction (PDB:6Q36). Linear (**43**) and (B) residue mutated peptide inhibitor (**44**).[40,238]

towards the Nrf2/Keap1 PPI achieving 10-fold improvement in hit rate over traditional HTS.[245]

Conclusion

Drug discovery on PPIs has wide ranging applications for disease management, often finding molecules with high specificity for target. The literature collated here provides a snapshot into the range of success in the inhibition of diverse types of PPI.

α-Helix mediated interactions are the most prominent secondary structure found within the proteome and participate in over 50% of the druggable PPIs presently investigated, describing helix-in-groove PPIs. Interestingly, coiled coils represent an underexplored PPI within helix-mediated PPI inhibitors. Utilising tools for helical mimetics or fragment-based drug discovery to design small molecules of these PPIs could offer a new method for targeted coiled coil interactions. β-strands, less common in overall protein content, were featured in 30% of PPIs with inhibitors. Strand-in-groove interactions have been described as more challenging to find hits against by HTS in comparison to helix-in-groove PPIs.[31] Alternative methods to fragment-based inhibitor discovery, such as peptide directed ligand design, may offer improved efficiency to small molecule design of β-strand PPIs.[211] The remaining interactions with inhibitors found are dynamic PPIs, including loops and IDR recognition sequences. Peptide inhibitors of β-strands and loop structures benefit from macrocyclisation techniques to stabilise the desired secondary structure, whilst also improving cell permeability and protection against degradation. Structure-based design of small molecules, guided by key PPI hotspot residues enables the development of potent inhibitors with nanomolar affinity for IDR PPIs. This rational SAR-driven approach is a promising direction for PPI drug discovery.

Despite advances in drug discovery, small molecule inhibitors across all categories of PPIs are still predominantly found by HTS, typically observing hits at rates lower than 1%.[246,247] Some HTS techniques use competition assays against peptide inhibitors derived from native PPI interfaces. Targeting hot-spot residues and sequences critical for binding, combined with fragment-based drug discovery, could afford greater selectivity and efficiency in small molecule design.[186–188,211] Additionally the use of techniques to screen large libraries of peptide sequences such as phage display, mRNA display or peptide arrays expands the potential for designing peptide inhibitors targeting both structured and unstructured PPIs.[248,249] There is an increasing abundance of structural data published depicting the secondary structures of PPIs, complemented by machine learning programs such as AlphaFold3 and RosettaFold, which can help to visualise challenging dynamic proteins in complex where crystal structure data is unavailable. Methods to identify PPI inhibitors rely on this structural data, and as such the inhibitors identified are skewed to the more stable interactions. The growth of structural biology methods such as Cryo-EM more readily allows for the characterisation of protein complexes, revealing

structural details about intrinsically disordered regions, and multiple protein partners. This data, coupled with protein complex structure prediction will rapidly increase the targets for inhibitor development. There remains a challenge to develop methods more suited to less well studied interactions, particularly IDRs and coiled coils. This review highlights the current imbalance in PPI inhibitor discovery when grouped by structural features. Interestingly, a limited number of inhibitors have been reported against intrinsically disordered regions, despite these structures being significantly represented at sites of known disease mutations.[250] Highlighting a need to develop inhibitors against PPIs without defined secondary structure.

Looking forward, the greatest opportunities in PPI drug discovery lie within underexplored interaction classes, particularly intrinsically disordered regions. Advances in cryo-EM, machine-learning-based structure prediction and AI-enabled ligand discovery are rapidly expanding the accessible PPI landscape. As structural coverage of the interactome grows, approaches that integrate peptide engineering, fragment-based discovery and computational design will be increasingly important for transforming currently intractable PPIs into tractable therapeutic targets. The structural framework presented here provides a basis for prioritising discovery strategies according to interface architecture and may help accelerate the development of future PPI therapeutics.

Author contributions

EEH: conceptualization, methodology, analysis, data curation, writing, visualization. AMB: conceptualization, data curation, writing, visualization.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support the information in this review article are found within the citations detailed in the reference list.

Acknowledgements

EEH and AMB acknowledge BBSRC NRPDTP for a PhD studentship (BB/T008717/1 - 2585701).

Notes and references

1 B. J. Mayer, *Methods Mol. Biol.*, 2006, **332**, 79–99.
2 A. Grigoriev, *Nucleic Acids Res.*, 2001, **29**, 3513–3519.
3 P. Durek and D. Walther, *BMC Syst. Biol.*, 2008, **2**, 100.
4 C. H. M. Rodrigues, D. E. V. Pires, T. L. Blundell and D. B. Ascher, *Brief. Bioinform.*, 2022, **23**, bbac165.
5 S. Das and S. Chakrabarti, *Sci. Rep.*, 2021, **11**, 1761.
6 K. Dhusia and Y. Wu, *BMC Bioinform.*, 2021, **22**, 408.
7 S. P. van Wier and A. M. Beekman, *Chem. Soc. Rev.*, 2025, **54**, 1684–1698.
8 S. Akbarzadeh, Ö. Coşkun and B. Günçer, *J. Struct. Biol.*, 2024, **216**, 108118.
9 H. Lu, Q. Zhou, J. He, Z. Jiang, C. Peng, R. Tong and J. Shi, *Signal Transduction Targeted Ther.*, 2020, **5**, 1–23.
10 S. S. Raj and S. S. V. Chandra, *Protein J.*, 2024, **43**, 72–83.
11 V. Neduva and R. B. Russell, *Curr. Opin. Biotechnol.*, 2006, **17**, 465–471.
12 E. Petsalaki and R. B. Russell, *Curr. Opin. Biotechnol.*, 2008, **19**, 344–350.
13 T. B. Thompson, P. Chaggar, E. Kuhl and A. Goriely, *PLoS Comput. Biol.*, 2020, **16**, e1008267.
14 M. Sharifi Tabar, H. Francis, D. Yeo, C. G. Bailey and J. E. J. Rasko, *Int. J. Cancer*, 2022, **151**, 7–19.
15 K. M. Poluri, K. Gulati, D. K. Tripathi and N. Nagar, in *Protein-Protein Interactions: Pathophysiological and Therapeutic Aspects*, ed. K. M. Poluri, K. Gulati, D. K. Tripathi and N. Nagar, Springer Nature, Singapore, 2023, vol. 2, pp. 171–206.
16 C. Ruiz, M. Zitnik and J. Leskovec, *Nat. Commun.*, 2021, **12**, 1796.
17 S. Stilgenbauer, B. Eichhorst, J. Schetelig, P. Hillmen, J. F. Seymour, S. Coutre, W. Jurczak, S. P. Mulligan, A. Schuh, S. Assouline, C.-M. Wendtner, A. W. Roberts, M. S. Davids, J. Bloehdorn, T. Munir, S. Böttcher, L. Zhou, A. H. Salem, M. Desai, B. Chyla, J. Arzt, S. Y. Kim, M. Verdugo, G. Gordon, M. Hallek and W. G. Wierda, *J. Clin. Oncol.*, 2018, **36**, 1973–1980.
18 H. Lu, Q. Zhou, J. He, Z. Jiang, C. Peng, R. Tong and J. Shi, *Signal Transduction Targeted Ther.*, 2020, **5**, 213.
19 Aileron Therapeutics, Inc., A Phase 1/2a Open-Label Study to Determine the Safety and Tolerability of ALRN-6924 Alone or in Combination in Patients With Advanced Solid Tumors or Lymphomas Expressing Wild-Type p53 Protein, 2026, https://clinicaltrials.gov/study/NCT02264613.
20 K. Luck, D.-K. Kim, L. Lambourne, K. Spirohn, B. E. Begg, W. Bian, R. Brignall, T. Cafarelli, F. J. Campos-Laborie, B. Charloteaux, D. Choi, A. G. Coté, M. Daley, S. Deimling, A. Desbuleux, A. Dricot, M. Gebbia, M. F. Hardy, N. Kishore, J. J. Knapp, I. A. Kovács, I. Lemmens, M. W. Mee, J. C. Mellor, C. Pollis, C. Pons, A. D. Richardson, S. Schlabach, B. Teeking, A. Yadav, M. Babor, D. Balcha, O. Basha, C. Bowman-Colin, S.-F. Chin, S. G. Choi, C. Colabella, G. Coppin, C. D'Amata, D. D. Ridder, S. D. Rouck, M. Duran-Frigola, H. Ennajdaoui, F. Goebels, L. Goehring, A. Gopal, G. Haddad, E. Hatchi, M. Helmy, Y. Jacob, Y. Kassa, S. Landini, R. Li, N. van Lieshout, A. MacWilliams, D. Markey, J. N. Paulson, S. Rangarajan, J. Rasla, A. Rayhan, T. Rolland, A. San-Miguel, Y. Shen, D. Sheykhkarimli, G. M. Sheynkman, E. Simonovsky, M. Taşan, A. Tejeda, V. Tropepe, J.-C. Twizere, Y. Wang, R. J. Weatheritt, J. Weile, Y. Xia, X. Yang, E. Yeger-Lotem, Q. Zhong, P. Aloy, G. D. Bader, J. D. L. Rivas, S. Gaudet, T. Hao, J. Rak, J. Tavernier, D. E. Hill, M. Vidal, F. P. Roth and M. A. Calderwood, *Nature*, 2020, **580**, 402–408.
21 X. Ran and J. E. Gestwicki, *Curr. Opin. Chem. Biol.*, 2018, **44**, 75–86.

 This journal is © The Royal Society of Chemistry 2026

22 J. Choi, J. S. Yun, H. Song, N. H. Kim, H. S. Kim and J. I. Yook, *Sci. Rep.*, 2021, **11**, 13369.
23 A. D. Thompson, A. Dugan, J. E. Gestwicki and A. K. Mapp, *ACS Chem. Biol.*, 2012, **7**, 1311–1320.
24 A. E. Modell, S. L. Blosser and P. S. Arora, *Trends Pharmacol. Sci.*, 2016, **37**, 702–713.
25 T. K. Neklesa, J. D. Winkler and C. M. Crews, *Pharmacol. Ther.*, 2017, **174**, 138–144.
26 S. Pathmanathan, I. Grozavu, A. Lyakisheva and I. Stagljar, *Curr. Opin. Chem. Biol.*, 2022, **66**, 102079.
27 M. M. R. Arkin and J. A. Wells, *Nat. Rev. Drug Discov.*, 2004, **3**, 301–317.
28 A. P. Higueruelo, H. Jubb and T. L. Blundell, *J. Biol. Databases Curation*, 2013, **2013**, bat039.
29 C. M. Labbé, G. Laconde, M. A. Kuenemann, B. O. Villoutreix and O. Sperandio, *Drug Discovery Today*, 2013, **18**, 958–968.
30 K. S. Thorn and A. A. Bogan, *Bioinformatics*, 2001, **17**, 284–285.
31 S. Celis, F. Hobor, T. James, G. J. Bartlett, A. A. Ibarra, D. K. Shoemark, Z. Hegedüs, K. Hetherington, D. N. Woolfson, R. B. Sessions, T. A. Edwards, D. M. Andrews, A. Nelson and A. J. Wilson, *Chem. Sci.*, 2021, **12**, 4753–4762.
32 A. L. Jochim and P. S. Arora, *Mol. BioSyst.*, 2009, **5**, 924–926.
33 B. N. Bullock, A. L. Jochim and P. S. Arora, *J. Am. Chem. Soc.*, 2011, **133**, 14220–14223.
34 M. C. Deller, L. Kong and B. Rupp, *Acta Crystallogr., Sect. F: Struct. Biol. Commun.*, 2016, **72**, 72–95.
35 W. N. Price, Y. Chen, S. K. Handelman, H. Neely, P. Manor, R. Karlin, R. Nair, J. Liu, M. Baran, J. Everett, S. N. Tong, F. Forouhar, S. S. Swaminathan, T. Acton, R. Xiao, J. R. Luft, A. Lauricella, G. T. DeTitta, B. Rost, G. T. Montelione and J. F. Hunt, *Nat. Biotechnol.*, 2009, **27**, 51–57.
36 A. M. Watkins and P. S. Arora, *ACS Chem. Biol.*, 2014, **9**, 1747–1754.
37 B. V. Reddy, H. A. Nagarajaram and T. L. Blundell, *Protein Sci.*, 1999, **8**, 573–586.
38 V. Perovic, N. Sumonja, L. A. Marsh, S. Radovanovic, M. Vukicevic, S. G. E. Roberts and N. Veljkovic, *Sci. Rep.*, 2018, **8**, 10563.
39 G. Kibar and M. Vingron, *Proteins: Struct., Funct., Bioinf.*, 2023, **91**, 980–990.
40 Z. Zhang, Z. Lin, Z. Zhou, H. C. Shen, S. F. Yan, A. V. Mayweg, Z. Xu, N. Qin, J. C. Wong, Z. Zhang, Y. Rong, D. C. Fry and T. Hu, *ACS Med. Chem. Lett.*, 2014, **5**, 993–998.
41 D. Yasuda, M. Nakajima, A. Yuasa, R. Obata, K. Takahashi, T. Ohe, Y. Ichimura, M. Komatsu, M. Yamamoto, R. Imamura, H. Kojima, T. Okabe, T. Nagano and T. Mashino, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5956–5959.
42 A. Mansilla, A. Chaves-Sanjuan, N. E. Campillo, O. Semelidou, L. Martínez-González, L. Infantes, J. M. González-Rubio, C. Gil, S. Conde, E. M. C. Skoulakis, A. Ferrús, A. Martínez and M. J. Sánchez-Barrena, *Proc. Natl. Acad. Sci. U. S. A.*, 2017, **114**, E999–E1008.
43 N. Qvit, A. U. Joshi, A. D. Cunningham, J. C. B. Ferreira and D. Mochly-Rosen, *J. Biol. Chem.*, 2016, **291**, 13608–13621.
44 M. Raj, B. N. Bullock and P. S. Arora, *Bioorg. Med. Chem.*, 2013, **21**, 4051–4057.
45 K. Wang, X. M. Yin, D. T. Chao, C. L. Milliman and S. J. Korsmeyer, *Genes Dev.*, 1996, **10**, 2859–2869.
46 M. Taniguchi, K.-I. Suzumura, K. Nagai, T. Kawasaki, J. Takasaki, M. Sekiguchi, Y. Moritani, T. Saito, K. Hayashi, S. Fujita, S.-I. Tsukamoto and K.-I. Suzuki, *Bioorg. Med. Chem.*, 2004, **12**, 3125–3133.
47 S. A. Kawamoto, A. Coleska, X. Ran, H. Yi, C.-Y. Yang and S. Wang, *J. Med. Chem.*, 2012, **55**, 1137–1146.
48 M. de la Roche, T. J. Rutherford, D. Gupta, D. B. Veprintsev, B. Saxty, S. M. Freund and M. Bienz, *Nat. Commun.*, 2012, **3**, 680.
49 H. Zhou, J. Lu, L. Liu, D. Bernard, C.-Y. Yang, E. Fernandez-Salas, K. Chinnaswamy, S. Layton, J. Stuckey, Q. Yu, W. Zhou, Z. Pan, Y. Sun and S. Wang, *Nat. Commun.*, 2017, **8**, 1150.
50 B. Wang, H. Yang, Y.-C. Liu, T. Jelinek, L. Zhang, E. Ruoslahti and H. Fu, *Biochemistry*, 1999, **38**, 12499–12504.
51 Z. Gao, Y. Tian, J. Wang, Q. Yin, H. Wu, Y.-M. Li and X. Jiang, *J. Biol. Chem.*, 2007, **282**, 30718–30727.
52 D. Sela, J. J. Conkright, L. Chen, J. Gilmore, M. P. Washburn, L. Florens, R. C. Conaway and J. W. Conaway, *J. Biol. Chem.*, 2013, **288**, 26179–26187.
53 H. Jiang, R. Deng, X. Yang, J. Shang, S. Lu, Y. Zhao, K. Song, X. Liu, Q. Zhang, Y. Chen, Y. E. Chinn, G. Wu, J. Li, G. Chen, J. Yu and J. Zhang, *Nat. Chem. Biol.*, 2017, **13**, 994–1001.
54 C. Garcia-Echeverria, P. Chene, M. J. J. Blommers and P. Furet, *J. Med. Chem.*, 2000, **43**, 3205–3208.
55 M. L. Stewart, E. Fire, A. E. Keating and L. D. Walensky, *Nat. Chem. Biol.*, 2010, **6**, 595–601.
56 S. Kushal, B. B. Lao, L. K. Henchey, R. Dubey, H. Mesallati, N. J. Traaseth, B. Z. Olenyuk and P. S. Arora, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, 15602–15607.
57 S. Jeganathan, M. Wendt, S. Kiehstaller, D. Brancaccio, A. Kuepper, N. Pospiech, A. Carotenuto, E. Novellino, S. Hennig and T. N. Grossmann, *Angew. Chem., Int. Ed.*, 2019, **58**, 17351–17358.
58 J. V. Frangioni, L. M. LaRiccia, L. C. Cantley and M. R. Montminy, *Nat. Biotechnol.*, 2000, **18**, 1080–1085.
59 I. M. Brooks and S. J. Tavalin, *J. Biol. Chem.*, 2011, **286**, 6697–6706.
60 W. Kim, G. H. Bird, T. Neff, G. Guo, M. A. Kerenyi, L. D. Walensky and S. H. Orkin, *Nat. Chem. Biol.*, 2013, **9**, 643–650.
61 P. 't Hart, P. Hommen, A. Noisier, A. Krzyzanowski, D. Schüler, A. T. Porfetye, M. Akbarzadeh, I. R. Vetter, H. Adihou and H. Waldmann, *Angew. Chem., Int. Ed.*, 2021, **60**, 1813–1820.
62 B. He, J. T. Minges, L. W. Lee and E. M. Wilson, *J. Biol. Chem.*, 2002, **277**, 10226–10235.
63 S. V. Maifeld, A. L. MacKinnon, J. L. Garrison, A. Sharma, E. J. Kunkel, R. S. Hegde and J. Taunton, *Chem. Biol.*, 2011, **18**, 1082–1088.
64 D. Peter, C. Igreja, R. Weber, L. Wohlbold, C. Weiler, L. Ebertsch, O. Weichenrieder and E. Izaurralde, *Mol. Cell*, 2015, **57**, 1074–1087.

65 J. Han, M. Yu, Y. Bai, J. Yu, F. Jin, C. Li, R. Zeng, J. Peng, A. Li, X. Song, H. Li, D. Wu and L. Li, *Cancer Cell*, 2020, **38**, 844–856.e7.

66 Y. Zheng, B.-S. Li, N. D. Amin, W. Albers and H. C. Pant, *Eur. J. Biochem.*, 2002, **269**, 4427–4434.

67 J. Chatterjee, M. Beullens, R. Sukackaite, J. Qian, B. Lesage, D. J. Hart, M. Bollen and M. Köhn, *Angew. Chem., Int. Ed.*, 2012, **51**, 10054–10059.

68 Y.-J. Kwon, B. A. Leibovitch, N. Bansal, L. Pereira, C.-Y. Chung, E. V. Ariztia, A. Zelent, E. F. Farias and S. Waxman, *Oncotarget*, 2016, **8**, 88421–88436.

69 Q. Li, C. Zeng, H. Liu, K. W. Y. Yung, C. Chen, Q. Xie, Y. Zhang, S. W. C. Wan, B. S. W. Mak, J. Xia, S. Xiong and J. C. K. Ngo, *iScience*, 2021, **24**, 102423.

70 Y. Gao, J. B. Dickerson, F. Guo, J. Zheng and Y. Zheng, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 7618–7623.

71 S. Ito, K. Ogawa, K. Takeuchi, M. Takagi, M. Yoshida, T. Hirokawa, S. Hirayama, K. Shin-ya, I. Shimada, T. Doi, N. Goshima, T. Natsume and K. Nagata, *J. Biol. Chem.*, 2017, **292**, 20076–20085.

72 T. Song, Y. Guo, Z. Xue, Z. Guo, Z. Wang, D. Lin, H. Zhang, H. Pan, X. Zhang, F. Yin, H. Wang, L. B. Uwituze and Z. Zhang, *Leukemia*, 2021, **35**, 2862–2874.

73 P. Li, Y. Tian, Q. Shang, C. Tang, Z. Hou, Y. Li, L. Cao, S. Xue, J. Bian, C. Luo, D. Wu, Z. Li and H. Ding, *Bioorg. Chem.*, 2023, **139**, 106676.

74 K. Huang and L. T. Vassilev, in *Methods in Enzymology*, Academic Press, 2005, vol. 399, pp. 717–728.

75 A. Beautrait, J. S. Paradis, B. Zimmerman, J. Giubilaro, L. Nikolajev, S. Armando, H. Kobayashi, L. Yamani, Y. Namkung, F. M. Heydenreich, E. Khoury, M. Audet, P. P. Roux, D. B. Veprintsev, S. A. Laporte and M. Bouvier, *Nat. Commun.*, 2017, **8**, 15054.

76 D. C. McKinney, B. J. McMillan, M. J. Ranaghan, J. A. Moroco, M. Brousseau, Z. Mullin-Bernstein, M. O'Keefe, P. McCarren, M. F. Mesleh, K. M. Mulvaney, F. Robinson, R. Singh, B. Bajrami, F. F. Wagner, R. Hilgraf, M. J. Drysdale, A. J. Campbell, A. Skepner, D. E. Timm, D. Porter, V. K. Kaushik, W. R. Sellers and A. Ianari, *J. Med. Chem.*, 2021, **64**, 11148–11168.

77 T. Furuya, J. Lin, A. Afanaseva, L. Molz, B. Lagu and B. Ma, *ACS Med. Chem. Lett.*, 2023, **14**, 1095–1099.

78 E. Robinson, E. Leung, A. M. Matuszek, N. Krogsgaard-Larsen, D. P. Furkert, M. A. Brimble, A. Richardson and J. Reynisson, *MedChemComm*, 2015, **6**, 239–246.

79 A. K. Farag, A. H. E. Hassan, H. Jeong, Y. Kwon, J. G. Choi, M. S. Oh, K. D. Park, Y. K. Kim and E. J. Roh, *Eur. J. Med. Chem.*, 2019, **162**, 161–175.

80 S.-S. Cheng, Y.-Q. Qu, J. Wu, G.-J. Yang, H. Liu, W. Wang, Q. Huang, F. Chen, G. Li, C.-Y. Wong, V. K. W. Wong, D.-L. Ma and C.-H. Leung, *Acta Pharm. Sin. B.*, 2022, **12**, 1390–1405.

81 J. Randjelovic, S. Eric and V. Savic, *J. Mol. Model.*, 2014, **50**, 100–112.

82 J. Randjelović, S. Erić and V. Savić, *J. Mol. Model.*, 2013, **19**, 1711–1725.

83 S. Taniguchi, Y. Ono, Y. Doi, S. Taniguchi, Y. Matsuura, A. Iwasaki, N. Hirata, R. Fukuda, K. Inoue, M. Yamaguchi, A. Tashiro, D. Egami, S. Aoki, Y. Kondoh, K. Honda, H. Osada, H. Kumeta, T. Saio and T. Okiyoneda, *Biochem. Pharmacol.*, 2023, **215**, 115730.

84 E. M. McNeil, K. R. Astell, A.-M. Ritchie, S. Shave, D. R. Houston, P. Bakrania, H. M. Jones, P. Khurana, C. Wallace, T. Chapman, M. A. Wear, M. D. Walkinshaw, B. Saxty and D. W. Melton, *DNA Repair*, 2015, **31**, 19–28.

85 L. Wang, L. Zhang, L. Li, J. Jiang, Z. Zheng, J. Shang, C. Wang, W. Chen, Q. Bao, X. Xu, Z. Jiang, J. Zhang and Q. You, *Sci. Adv.*, 2019, **5**, eaax2277.

86 S. Sayedyahossein, J. Smith, E. Barnaeva, Z. Li, J. Choe, M. Ronzetti, C. Dextras, X. Hu, J. Marugan, N. Southall, B. Baljinnyam, L. Thines, A. D. Tran, M. Ferrer and D. B. Sacks, *Sci. Rep.*, 2022, **12**, 17372.

87 X. Jin, Y. Yang, D. Liu, X. Zhou and Y. Huang, *Cell Commun. Signal.*, 2024, **22**, 565.

88 G. Menchon, O. Bombarde, M. Trivedi, A. Négrel, C. Inard, B. Giudetti, M. Baltas, A. Milon, M. Modesti, G. Czaplicki and P. Calsou, *Sci. Rep.*, 2016, **6**, 22878.

89 Y. Fang, X. Chen, Q. Tan, H. Zhou, J. Xu and Q. Gu, *ACS Cent. Sci.*, 2021, **7**, 980–989.

90 J. Gu, R.-K. Peng, C.-L. Guo, M. Zhang, J. Yang, X. Yan, Q. Zhou, H. Li, N. Wang, J. Zhu and Q. Ouyang, *Nat. Commun.*, 2022, **13**, 7176.

91 J. Nong, S. Shen, F. Hong, F. Xiao, L. Meng, P. Li, X. Lei and Y.-G. Chen, *Mol. Biol. Cell*, 2024, **35**, ar95.

92 J. M. Mason, M. A. Schmitz, K. M. Müller and K. M. Arndt, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8989–8994.

93 J. K.-L. Sinclair, E. V. Denton and A. Schepartz, *J. Am. Chem. Soc.*, 2014, **136**, 11232–11235.

94 K. M. Hawley, R. J. Eclov, M. R. Schnorenberg, Y. Tian, R. N. Shah, A. T. Thomas-Toth, M. Fefferman, G. H. Bird, L. D. Walensky, M. V. Tirrell and J. L. LaBelle, *Proc. Natl. Acad. Sci. U. S. A.*, 2022, **119**, e2209044119.

95 M. O. Okpara, M. C. Vaaltyn, J. L. Watson, M. Alhassan, F. Albericio, B. G. de la Torre, D. J. Clarke, C. G. L. Veale and A. L. Edkins, *ACS Infect. Dis.*, 2024, **10**, 3853–3867.

96 J. Speck, C. Räuber, T. Kükenshöner, C. Niemöller, K. J. Mueller, P. Schleberger, P. Dondapati, J. Hecky, K. M. Arndt and K. M. Müller, *Protein Eng., Des. Sel.*, 2013, **26**, 225–242.

97 X. Ran, E. T. Burchfiel, B. Dong, N. J. Rettko, B. M. Dunyak, H. Shao, D. J. Thiele and J. E. Gestwicki, *Bioorg. Med. Chem.*, 2018, **26**, 5299–5306.

98 R. Modi, N. McKee, N. Zhang, A. Alwali, S. Nelson, A. Lohar, R. Ostafe, D. D. Zhang and E. I. Parkinson, *J. Med. Chem.*, 2023, **66**, 6184–6192.

99 T. Berg, S. B. Cohen, J. Desharnais, C. Sonderegger, D. J. Maslyar, J. Goldberg, D. L. Boger and P. K. Vogt, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 3830–3835.

100 H. M. Dickson, A. Wilbur, A. A. Reinke, M. A. Young and A. B. Vojtek, *BMC Neurosci.*, 2015, **16**, 34.

101 M. Y. Kim, I. Na, J. S. Kim, S. H. Son, S. Choi, S. E. Lee, J.-H. Kim, K. Jang, G. Alterovitz, Y. Chen, A. van der Vaart, H.-S. Won, V. N. Uversky and C. G. Kim, *Sci. Adv.*, 2019, **5**, eaav9810.

 This journal is © The Royal Society of Chemistry 2026

102 I. Pavlinov, M. Salkovski and L. N. Aldrich, *J. Am. Chem. Soc.*, 2020, **142**, 8174–8182.

103 S. B. Petkova, S. Akilesh, T. J. Sproule, G. J. Christianson, H. Al Khabbaz, A. C. Brown, L. G. Presta, Y. G. Meng and D. C. Roopenian, *Int. Immunol.*, 2006, **18**, 1759–1769.

104 J. Hemelaar, A. Borodovsky, B. M. Kessler, D. Reverter, J. Cook, N. Kolli, T. Gan-Erdene, K. D. Wilkinson, G. Gill, C. D. Lima, H. L. Ploegh and H. Ovaa, *Mol. Cell. Biol.*, 2004, **24**, 84–95.

105 M. C. Hammond, B. Z. Harris, W. A. Lim and P. A. Bartlett, *Chem. Biol.*, 2006, **13**, 1247–1251.

106 M. O. Gray, J. S. Karliner and D. Mochly-Rosen, *J. Biol. Chem.*, 1997, **272**, 30945–30951.

107 A. Lesner, A. Legowska, M. Wysocka and K. Rolka, *Curr. Pharm. Des.*, 2011, **17**, 4308–4317.

108 Y. Zhang, C. Eigenbrot, L. Zhou, S. Shia, W. Li, C. Quan, J. Tom, P. Moran, P. Di Lello, N. J. Skelton, M. Kong-Beltran, A. Peterson and D. Kirchhofer, *J. Biol. Chem.*, 2014, **289**, 942–955.

109 C. R. O. Bartling, T. M. T. Jensen, S. M. Henry, A. L. Colliander, V. Sereikaite, M. Wenzler, P. Jain, H. M. Maric, K. Harpsøe, S. W. Pedersen, L. S. Clemmensen, L. M. Haugaard-Kedström, D. E. Gloriam, A. Ho and K. Strømgaard, *J. Am. Chem. Soc.*, 2021, **143**, 891–901.

110 J. Nomme, A. Renodon-Cornière, Y. Asanomi, K. Sakaguchi, A. Z. Stasiak, A. Stasiak, B. Norden, V. Tran and M. Takahashi, *J. Med. Chem.*, 2010, **53**, 5782–5791.

111 D. Kutscher, A. Pingoud, A. Jeltsch and G. Meiss, *FEBS J.*, 2012, **279**, 2917–2928.

112 W. C. Lee, S. Almeida, M. Prudencio, T. R. Caulfield, Y.-J. Zhang, W. M. Tay, P. O. Bauer, J. Chew, H. Sasaguri, K. R. Jansen-West, T. F. Gendron, C. T. Stetler, N. Finch, I. R. Mackenzie, R. Rademakers, F.-B. Gao and L. Petrucelli, *Hum. Mol. Genet.*, 2014, **23**, 1467–1478.

113 S. Chia, Z. Faidon Brotzakis, R. I. Horne, A. Possenti, B. Mannini, R. Cataldi, M. Nowinska, R. Staats, S. Linse, T. P. J. Knowles, J. Habchi and M. Vendruscolo, *Mol. Pharmaceutics*, 2023, **20**, 183–193.

114 T. Sameshima, T. Yamamoto, O. Sano, S. Sogabe, S. Igaki, K. Sakamoto, K. Ida, M. Gotou, Y. Imaeda, J. Sakamoto and I. Miyahisa, *Biochemistry*, 2018, **57**, 1369–1379.

115 J. Kastl, J. Braun, A. Prestel, H. M. Möller, T. Huhn and T. U. Mayer, *ACS Chem. Biol.*, 2015, **10**, 1661–1666.

116 M. Garcia, L. Hoffer, R. Leblanc, F. Benmansour, M. Feracci, C. Derviaux, A. L. Egea-Jimenez, P. Roche, P. Zimmermann, X. Morelli and K. Barral, *Eur. J. Med. Chem.*, 2021, **223**, 113601.

117 A. J. da Silva, M. Brickelmaier, G. R. Majeau, Z. Li, L. Su, Y.-M. Hsu and P. S. Hochman, *J. Immunol.*, 2002, **168**, 4462–4471.

118 T. T. Mai, P. G. Nguyen, M.-T. Le, T.-D. Tran, P. N. H. Huynh, D.-T. T. Trinh, Q.-T. Nguyen and K.-M. Thai, *Mol. Diversity*, 2022, **26**, 2659–2678.

119 J. C. Chavez, F. M. Foss, B. M. William, J. E. Brammer, S. M. Smith, A. Prica, J. M. Zain, J. M. Tuscano, M. Glenn, N. Mehta-Shah, B. X. Wang, S. Zantinge, L. Wang, L. Zhang, A. Boutrin, W. Zhao, L. Cheng, N. Standifer, G. Carlesso, J. Moscow and L. Siu, *Blood*, 2020, **136**, 5–6.

120 D. J. Marcotte, J. Hus, C. C. Banos, C. Wildes, R. Arduini, C. Bergeron, C. A. Hession, D. P. Baker, E. Lin, K. M. Guckian, A. W. Dunah and L. F. Silvian, *Protein Sci.*, 2018, **27**, 672–680.

121 H. Kobayashi, J. Gotoh, M. Fujie, H. Shinohara, N. Moniwa and T. Terao, *Int. J. Cancer*, 1994, **57**, 727–733.

122 H. M. Ta, G. T. T. Nguyen, H. M. Jin, J. Choi, H. Park, N. Kim, H.-Y. Hwang and K. K. Kim, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20281–20286.

123 P. G. N. Sasikumar and M. Ramachandra, *World Intellectual Property Organization Pat.*, WO2013144704A1, 2013.

124 K. Wichapong, J.-E. Alard, A. Ortega-Gomez, C. Weber, T. M. Hackeng, O. Soehnlein and G. A. F. Nicolaes, *J. Med. Chem.*, 2016, **59**, 4289–4301.

125 J. Rahuel, B. Gay, D. Erdmann, A. Strauss, C. Garcia-Echeverría, P. Furet, G. Caravatti, H. Fretz, J. Schoepfer and M. G. Grütter, *Nat. Struct. Biol.*, 1996, **3**, 586–589.

126 S. L. Alexander, T. F. Briggs, F. G. F. Jr, S. P. Hale, B. A. Seigal, K. C. Shortsleeves, C. Snedeker, M. Taylor, N. K. Terrett, D. Yan, P. W. Nowak, R. A. Denny, B. A. Chrunyk, P. V. Sahasrabudhe and J. M. Withka, *World Intellectual Property Organization Pat.*, WO2014066726A2, 2014.

127 M. M. He, A. S. Smith, J. D. Oslob, W. M. Flanagan, A. C. Braisted, A. Whitty, M. T. Cancilla, J. Wang, A. A. Lugovskoy, J. C. Yoburn, A. D. Fung, G. Farrington, J. K. Eldredge, E. S. Day, L. A. Cruz, T. G. Cachero, S. K. Miller, J. E. Friedman, I. C. Choong and B. C. Cunningham, *Science*, 2005, **310**, 1022–1025.

128 S. Florio, C. Loh, S. Huang, A. Iwamaye, K. Kitto, K. Fowler, J. Treiberg, J. Hayflick, J. Walker, C. Fairbanks and Y. Lai, *Br. J. Pharmacol.*, 2009, **158**, 494–506.

129 A. Illendula, J. A. Pulikkan, H. Zong, J. Grembecka, L. Xue, S. Sen, Y. Zhou, A. Boulton, A. Kuntimaddi, Y. Gao, R. A. Rajewski, M. L. Guzman, L. H. Castilla and J. H. Bushweller, *Science*, 2015, **347**, 779–784.

130 F. Cai, Y. Huang, M. Wang, M. Sun, Y. Zhao and M. Hattori, *Sci. Rep.*, 2020, **10**, 12879.

131 B. Yakubov, L. Chen, A. M. Belkin, S. Zhang, B. Chelladurai, Z.-Y. Zhang and D. Matei, *PLoS One*, 2014, **9**, e89285.

132 C. E. Quevedo, A. Cruz-Migoni, N. Bery, A. Miller, T. Tanaka, D. Petch, C. J. R. Bataille, L. Y. W. Lee, P. S. Fallon, H. Tulmin, M. T. Ehebauer, N. Fernandez-Fuentes, A. J. Russell, S. B. Carr, S. E. V. Phillips and T. H. Rabbitts, *Nat. Commun.*, 2018, **9**, 3169.

133 S.-C. Lo, X. Li, M. T. Henzl, L. J. Beamer and M. Hannink, *EMBO J.*, 2006, **25**, 3605–3617.

134 A. D. Abell, M. A. Jones, J. M. Coxon, J. D. Morton, S. G. Aitken, S. B. McNabb, H. Y.-Y. Lee, J. M. Mehrtens, N. A. Alexander, B. G. Stuart, A. T. Neffe and R. Bickerstaffe, *Angew. Chem., Int. Ed.*, 2009, **48**, 1455–1458.

135 J. Grembecka, A. M. Belcher, T. Hartley and T. Cierpicki, *J. Biol. Chem.*, 2010, **285**, 40690–40698.

136 O. V. Tsodikov, D. Ivanov, B. Orelli, L. Staresincic, I. Shoshani, R. Oberman, O. D. Schärer, G. Wagner and T. Ellenberger, *EMBO J.*, 2007, **26**, 4768–4776.

137 H. Karatas, E. C. Townsend, D. Bernard, Y. Dou and S. Wang, *J. Med. Chem.*, 2010, **53**, 5179–5185.

138 T. Saito, Y. Ichimura, K. Taguchi, T. Suzuki, T. Mizushima, K. Takagi, Y. Hirose, M. Nagahashi, T. Iso, T. Fukutomi, M. Ohishi, K. Endo, T. Uemura, Y. Nishito, S. Okuda, M. Obata, T. Kouno, R. Imamura, Y. Tada, R. Obata, D. Yasuda, K. Takahashi, T. Fujimura, J. Pi, M.-S. Lee, T. Ueno, T. Ohe, T. Mashino, T. Wakai, H. Kojima, T. Okabe, T. Nagano, H. Motohashi, S. Waguri, T. Soga, M. Yamamoto, K. Tanaka and M. Komatsu, *Nat. Commun.*, 2016, **7**, 12030.

139 R. Fernández-Ginés, J. A. Encinar, J. D. Hayes, B. Oliva, M. I. Rodríguez-Franco, A. I. Rojo and A. Cuadrado, *Redox Biol.*, 2022, **55**, 102396.

140 A. Poissonnier, J.-P. Guégan, H. T. Nguyen, D. Best, N. Levoin, G. Kozlov, K. Gehring, R. Pineau, F. Jouan, L. Morere, S. Martin, M. Thomas, E. Lazaro, I. Douchet, T. Ducret, P. van de Weghe, P. Blanco, M. Jean, P. Vacher and P. Legembre, *Nat. Chem. Biol.*, 2018, **14**, 1079–1089.

141 A. E. H. Elia, L. C. Cantley and M. B. Yaffe, *Science*, 2003, **299**, 1228–1231.

142 B. H. Liu, C. Jobichen, C. S. B. Chia, T. H. M. Chan, J. P. Tang, T. X. Y. Chung, J. Li, A. Poulsen, A. W. Hung, X. Koh-Stenta, Y. S. Tan, C. S. Verma, H. K. Tan, C.-S. Wu, F. Li, J. Hill, J. Joy, H. Yang, L. Chai, J. Sivaraman and D. G. Tenen, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, E7119–E7128.

143 V. Sail, A. A. Rizzo, N. Chatterjee, R. C. Dash, Z. Ozen, G. C. Walker, D. M. Korzhnev and M. K. Hadden, *ACS Chem. Biol.*, 2017, **12**, 1903–1912.

144 S. Nim, D. M. O'Hara, C. Corbi-Verge, A. Perez-Riba, K. Fujisawa, M. Kapadia, H. Chau, F. Albanese, G. Pawar, M. L. De Snoo, S. G. Ngana, J. Kim, O. M. A. El-Agnaf, E. Rennella, L. E. Kay, S. K. Kalia, L. V. Kalia and P. M. Kim, *Nat. Commun.*, 2023, **14**, 2150.

145 C. Punchihewa, A. Inoue, A. Hishiki, Y. Fujikawa, M. Connelly, B. Evison, Y. Shao, R. Heath, I. Kuraoka, P. Rodrigues, H. Hashimoto, M. Kawanishi, M. Sato, T. Yagi and N. Fujii, *J. Biol. Chem.*, 2012, **287**, 14289–14300.

146 Z. Na, B. Peng, S. Ng, S. Pan, J.-S. Lee, H.-M. Shen and S. Q. Yao, *Angew. Chem., Int. Ed.*, 2015, **54**, 2515–2519.

147 S. M. Ø. Solbak, J. Zang, D. Narayanan, L. J. Høj, S. Bucciarelli, C. Softley, S. Meier, A. E. Langkilde, C. H. Gotfredsen, M. Sattler and A. Bach, *J. Med. Chem.*, 2020, **63**, 1156–1177.

148 J. Bennett, O. Fedorov, C. Tallant, O. Monteiro, J. Meier, V. Gamble, P. Savitsky, G. A. Nunez-Alonso, B. Haendler, C. Rogers, P. E. Brennan, S. Müller and S. Knapp, *J. Med. Chem.*, 2016, **59**, 1642–1647.

149 A. Coluccia, G. La Regina, V. Naccarato, M. Nalli, V. Orlando, S. Biagioni, M. L. De Angelis, M. Baiocchi, C. Gautier, S. Gianni, F. Di Pastena, L. Di Magno, G. Canettieri, A. M. L. Coluccia and R. Silvestri, *ACS Med. Chem. Lett.*, 2019, **10**, 499–503.

150 L. Han, J. B. Lee, E. W. Indermaur and A. J. Keung, *Biochem. J.*, 2023, **480**, 421–432.

151 P. G. K. Clark, L. C. C. Vieira, C. Tallant, O. Fedorov, D. C. Singleton, C. M. Rogers, O. P. Monteiro, J. M. Bennett, R. Baronio, S. Müller, D. L. Daniels, J. Méndez, S. Knapp, P. E. Brennan and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2015, **54**, 6217–6221.

152 S. Lim, H. Y. Cho, D. G. Kim, Y. Roh, S.-Y. Son, A. U. Mushtaq, M. Kim, D. Bhattarai, A. Sivaraman, Y. Lee, J. Lee, W. S. Yang, H. K. Kim, M. H. Kim, K. Lee, Y. H. Jeon and S. Kim, *Nat. Chem. Biol.*, 2020, **16**, 31–41.

153 M. Hisada, M. Hiranuma, M. Nakashima, N. Goda, T. Tenno and H. Hiroaki, *Eur. J. Pharmacol.*, 2020, **887**, 173436.

154 S.-Y. Hwang, S. Park, H. Jo, S. Hee Seo, K.-H. Jeon, S. Kim, A.-R. Jung, C. Song, M. Ahn, S. Yeon Kwak, H.-J. Lee, M. Uesugi, Y. Na and Y. Kwon, *J. Adv. Res.*, 2023, **47**, 173–187.

155 B. B. Lao, K. Drew, D. A. Guarracino, T. F. Brewer, D. W. Heindel, R. Bonneau and P. S. Arora, *J. Am. Chem. Soc.*, 2014, **136**, 7877–7888.

156 H. I. Merritt, N. Sawyer and P. S. Arora, *Peptide Sci.*, 2020, **112**, e24145.

157 P. H. Kussie, S. Gorina, V. Marechal, B. Elenbaas, J. Moreau, A. J. Levine and N. P. Pavletich, *Science*, 1996, **274**, 948–953.

158 S. Baek, P. S. Kutchukian, G. L. Verdine, R. Huber, T. A. Holak, K. W. Lee and G. M. Popowicz, *J. Am. Chem. Soc.*, 2012, **134**, 103–106.

159 O. Schon, A. Friedler, M. Bycroft, S. M. V. Freund and A. R. Fersht, *J. Mol. Biol.*, 2002, **323**, 491–501.

160 S. Shangary and D. E. Johnson, *Biochemistry*, 2002, **41**, 9485–9495.

161 E. F. Lee, A. Fedorova, K. Zobel, M. J. Boyle, H. Yang, M. A. Perugini, P. M. Colman, D. C. S. Huang, K. Deshayes and W. D. Fairlie, *J. Biol. Chem.*, 2009, **284**, 31315–31326.

162 S. Dutta, S. Gullá, T. S. Chen, E. Fire, R. A. Grant and A. E. Keating, *J. Mol. Biol.*, 2010, **398**, 747–762.

163 T. Maculins, J. Garcia-Pardo, A. Skenderovic, J. Gebel, M. Putyrski, A. Vorobyov, P. Busse, G. Varga, M. Kuzikov, A. Zaliani, S. Rahighi, V. Schaeffer, M. J. Parnham, S. S. Sidhu, A. Ernst, V. Dötsch, M. Akutsu and I. Dikic, *Cell Chem. Biol.*, 2020, **27**, 1441–1451.e7.

164 G. N. Sundell and Y. Ivarsson, *BioMed Res. Int.*, 2014, **2014**, 176172.

165 E. T. Boder and K. D. Wittrup, *Nat. Biotechnol.*, 1997, **15**, 553–557.

166 D. P. Hernandez and G. Dittmar, *Anal. Bioanal. Chem.*, 2021, **413**, 5561–5566.

167 D. Iaculli and S. Ballet, *J. Pept. Sci.*, 2025, **31**, e70029.

168 M. Pazgier, M. Liu, G. Zou, W. Yuan, C. Li, C. Li, J. Li, J. Monbo, D. Zella, S. G. Tarasov and W. Lu, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4665–4670.

169 C. Li, M. Pazgier, C. Li, W. Yuan, M. Liu, G. Wei, W.-Y. Lu and W. Lu, *J. Mol. Biol.*, 2010, **398**, 200–213.

170 M. Liu, M. Pazgier, C. Li, W. Yuan, C. Li and W. Lu, *Angew. Chem., Int. Ed.*, 2010, **49**, 3649–3652.

171 H. Yin, G. Lee, H. S. Park, G. A. Payne, J. M. Rodriguez, S. M. Sebti and A. D. Hamilton, *Angew. Chem., Int. Ed.*, 2005, **44**, 2704–2707.

172 J. P. Plante, T. Burnley, B. Malkova, M. E. Webb, S. L. Warriner, T. A. Edwards and A. J. Wilson, *Chem. Commun.*, 2009, 5091–5093.

173 J. H. Lee, Q. Zhang, S. Jo, S. C. Chai, M. Oh, W. Im, H. Lu and H.-S. Lim, *J. Am. Chem. Soc.*, 2010, **133**, 676–679.

 This journal is © The Royal Society of Chemistry 2026

174 B. B. Lao, K. Drew, D. A. Guarracino, T. F. Brewer, D. W. Heindel, R. Bonneau and P. S. Arora, *J. Am. Chem. Soc.*, 2014, **136**, 7877–7888.

175 M. Marciniak, P. Mróz, V. Napolitano, V. C. Kalel, R. Fino, E. Pykacz, W. Schliebs, O. Plettenburg, R. Erdmann, M. Sattler, G. M. Popowicz and M. Dawidowski, *Eur. J. Med. Chem.*, 2023, **258**, 115587.

176 P. Tošovská and P. S. Arora, *Org. Lett.*, 2010, **12**, 1588–1591.

177 S. Marimganti, M. N. Cheemala and J.-M. Ahn, *Org. Lett.*, 2009, **11**, 4418–4421.

178 C. Sheng, G. Dong, Z. Miao, W. Zhang and W. Wang, *Chem. Soc. Rev.*, 2015, **44**, 8238–8259.

179 I. Saraogi and A. D. Hamilton, *Biochem. Soc. Trans.*, 2008, **36**, 1414–1417.

180 C. Neufeld, F. V. Filipp, B. Simon, A. Neuhaus, N. Schüller, C. David, H. Kooshapur, T. Madl, R. Erdmann, W. Schliebs, M. Wilmanns and M. Sattler, *EMBO J.*, 2009, **28**, 745–754.

181 M. Marciniak, P. Mróz, V. Napolitano, V. C. Kalel, R. Fino, E. Pykacz, W. Schliebs, O. Plettenburg, R. Erdmann, M. Sattler, G. M. Popowicz and M. Dawidowski, *Eur. J. Med. Chem.*, 2023, **258**, 115587.

182 A. L. Rodriguez, A. Tamrazi, M. L. Collins and J. A. Katzenellenbogen, *J. Med. Chem.*, 2004, **47**, 600–611.

183 S. Kortagere, W. J. Welsh, J. M. Morrisey, T. Daly, I. Ejigiri, P. Sinnis, A. B. Vaidya and L. W. Bergman, *J. Chem. Inf. Model.*, 2010, **50**, 840–849.

184 C. H. Douse, J. L. Green, P. S. Salgado, P. J. Simpson, J. C. Thomas, G. Langsley, A. A. Holder, E. W. Tate and E. Cota, *J. Biol. Chem.*, 2012, **287**, 36968–36977.

185 J. Bosch, S. Turley, T. M. Daly, S. M. Bogh, M. L. Villasmil, C. Roach, N. Zhou, J. M. Morrisey, A. B. Vaidya, L. W. Bergman and W. G. J. Hol, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 4852–4857.

186 M. J. I. Andrews, G. Kontopidis, C. McInnes, A. Plater, L. Innes, A. Cowan, P. Jewsbury and P. M. Fischer, *Eur. J. Cell Biol.*, 2006, **7**, 1909–1915.

187 A. M. Beekman, M. A. O'Connell and L. A. Howell, *Angew. Chem., Int. Ed.*, 2017, **56**, 10446–10450.

188 A. M. Beekman, M. M. D. Cominetti, S. J. Walpole, S. Prabhu, M. A. O'Connell, J. Angulo and M. Searcey, *Chem. Sci.*, 2019, **10**, 4502–4508.

189 L. A. Howell and A. M. Beekman, *RSC Chem. Biol.*, 2021, **2**, 215–219.

190 F. H. C. Crick, *Nature*, 1952, **170**, 882–883.

191 L. Truebestein and T. A. Leonard, *BioEssays*, 2016, **38**, 903.

192 E. M. Jouaux, K. Schmidtkunz, K. M. Müller and K. M. Arndt, *J. Pept. Sci.*, 2008, **14**, 1022–1031.

193 H. Domingues, D. Cregut, W. Sebald, H. Oschkinat and L. Serrano, *Nat. Struct. Biol.*, 1999, **6**, 652–656.

194 J. M. Mason, K. M. Müller and K. M. Arndt, *Biochemistry*, 2007, **46**, 4804–4814.

195 K. E. Thompson, C. J. Bashor, W. A. Lim and A. E. Keating, *ACS Synth. Biol.*, 2012, **1**, 118–129.

196 J. M. Fletcher, K. A. Horner, G. J. Bartlett, G. G. Rhys, A. J. Wilson and D. N. Woolfson, *Chem. Sci.*, 2018, **9**, 7656–7665.

197 A. W. Reinke, R. A. Grant and A. E. Keating, *J. Am. Chem. Soc.*, 2010, **132**, 6025–6031.

198 G. Grigoryan, A. W. Reinke and A. E. Keating, *Nature*, 2009, **458**, 859–864.

199 C. W. Wood and D. N. Woolfson, *Protein Sci.*, 2018, **27**, 103–111.

200 L. Lu, F. Yu, L. Cai, A. K. Debnath and S. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1074–1090.

201 J. R. Hart, A. L. Garner, J. Yu, Y. Ito, M. Sun, L. Ueno, J.-K. Rhee, M. M. Baksh, E. Stefan, M. Hartl, K. Bister, P. K. Vogt and K. D. Janda, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, 12556–12561.

202 J. Chauhan, H. Wang, J. L. Yap, P. E. Sabato, A. Hu, E. V. Prochownik and S. Fletcher, *ChemMedChem*, 2014, **9**, 2274–2285.

203 I. Pavlinov, M. Salkovski and L. N. Aldrich, *Autophagy*, 2020, **16**, 1547–1549.

204 O. Khakshoor and J. S. Nowick, *Curr. Opin. Chem. Biol.*, 2008, **12**, 722–729.

205 D. Eisenberg, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 11207–11210.

206 G. Bellesia and J.-E. Shea, *J. Chem. Phys.*, 2009, **130**, 145103.

207 A. C. Tsolis, N. C. Papandreou, V. A. Iconomidou and S. J. Hamodrakas, *PLoS One*, 2013, **8**, e54175.

208 A. T. Namanja, Y.-J. Li, Y. Su, S. Wong, J. Lu, L. T. Colson, C. Wu, S. S. C. Li and Y. Chen, *J. Biol. Chem.*, 2012, **287**, 3231–3240.

209 E. E. Cawood, E. Baker, T. A. Edwards, D. N. Woolfson, T. K. Karamanos and A. J. Wilson, *Chem. Sci.*, 2024, **15**, 10237–10245.

210 L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang and C. Fu, *Signal Transduction Targeted Ther.*, 2022, **7**, 1–27.

211 Z. Hegedüs, F. Hóbor, D. K. Shoemark, S. Celis, L.-Y. Lian, C. H. Trinh, R. B. Sessions, T. A. Edwards and A. J. Wilson, *Chem. Sci.*, 2021, **12**, 2286–2293.

212 Q. Zhang, L. Yan, Y. Zhang, L. Zhang, J. Yu, Q. You and L. Wang, *Future Med. Chem.*, 2024, **16**, 125–138.

213 J. Kastl, J. Braun, A. Prestel, H. M. Möller, T. Huhn and T. U. Mayer, *ACS Chem. Biol.*, 2015, **10**, 1661–1666.

214 V. E. Albrow, E. L. Ponder, D. Fasci, M. Békés, E. Deu, G. S. Salvesen and M. Bogyo, *Chem. Biol.*, 2011, **18**, 722–732.

215 C. W. Robinson, C. S. Rye, N. E. A. Chessum and K. Jones, *Org. Biomol. Chem.*, 2015, **13**, 7402–7407.

216 J. Zang, F. Peters, Y. Cambet, E. Cifuentes-Pagano, M. M. S. Hissabu, C. M. Dustin, L. H. Svensson, M. M. Olesen, M. F. L. Poulsen, S. Jacobsen, P. S. Tuelung, D. Narayanan, A. E. Langkilde, M. Gajhede, P. J. Pagano, V. Jaquet, F. Vilhardt and A. Bach, *J. Med. Chem.*, 2023, **66**, 14963–15005.

217 W.-J. Jeong, J. Bu, Y. Han, A. J. Drelich, A. Nair, P. Král and S. Hong, *J. Am. Chem. Soc.*, 2020, **142**, 1832–1837.

218 M. Bojko, K. Węgrzyn, E. Sikorska, M. Kocikowski, M. Parys, C. Battin, P. Steinberger, M. M. Kogut, M. Winnicki, A. K. Sieradzan, M. Spodzieja and S. Rodziewicz-Motowidło, *Bioorg. Chem.*, 2022, **128**, 106047.

219 D. Hayward, Z. R. Goddard, M. M. D. Cominetti, M. Searcey and A. M. Beekman, *Chem. Commun.*, 2024, **60**, 8228–8231.

220 K. Wang, Y. Song, Y. Su, Y. Liang and L. Wang, *Biochem. Biophys. Res. Commun.*, 2020, **527**, 453–457.

221 L. Calvo-Barreiro, M. Secor, J. Damjanovic, S. A. Abdel-Rahman, Y.-S. Lin and M. Gabr, *Chem. Biol. Drug Des.*, 2025, **105**, e70117.

222 S. Bothe, P. Hänzelmann, S. Böhler, J. Kehrein, M. Zehe, C. Wiedemann, U. A. Hellmich, R. Brenk, H. Schindelin and C. Sotriffer, *Commun. Chem.*, 2022, **5**, 1–15.

223 Z. M. Oo, A. Illendula, J. Grembecka, C. Schmidt, Y. Zhou, V. Esain, W. Kwan, I. Frost, T. E. North, R. A. Rajewski, N. A. Speck and J. H. Bushweller, *Leuk. Lymphoma*, 2018, **59**, 2188–2200.

224 H. Mouhsine, H. Guillemain, G. Moreau, N. Fourati, C. Zerrouki, B. Baron, L. Desallais, P. Gizzi, N. Ben Nasr, J. Perrier, R. Ratsimandresey, J.-L. Spadoni, H. Do, P. England, M. Montes and J.-F. Zagury, *Sci. Rep.*, 2017, **7**, 3424.

225 S. A. Abdel-Rahman and M. T. Gabr, *SLAS Discov.*, 2025, **34**, 100240.

226 Y. J. Im, L. Kuo, X. Ren, P. V. Burgos, X. Z. Zhao, F. Liu, T. R. Burke, J. S. Bonifacino, E. O. Freed and J. H. Hurley, *Structure*, 2010, **18**, 1536–1547.

227 X. Yang, K. R. Lennard, C. He, M. C. Walker, A. T. Ball, C. Doigneaux, A. Tavassoli and W. A. van der Donk, *Nat. Chem. Biol.*, 2018, **14**, 375–380.

228 Z. Na, S. Pan, M. Uttamchandani and S. Q. Yao, in *Small Molecule Microarrays: Methods and Protocols*, ed. M. Uttamchandani and S. Q. Yao, Springer, New York, NY, 2017, pp. 139–156.

229 Y. M. Foong, J. Fu, S. Q. Yao and M. Uttamchandani, *Curr. Opin. Chem. Biol.*, 2012, **16**, 234–242.

230 C. H. S. Lu, H. Sun, F. B. Abu Bakar, M. Uttamchandani, W. Zhou, Y.-C. Liou and S. Q. Yao, *Angew. Chem., Int. Ed.*, 2008, **47**, 7438–7441.

231 M. Jung, M. Philpott, S. Müller, J. Schulze, V. Badock, U. Eberspächer, D. Moosmayer, B. Bader, N. Schmees, A. Fernández-Montalván and B. Haendler, *J. Biol. Chem.*, 2014, **289**, 9304–9319.

232 P. Filippakopoulos, J. Qi, S. Picaud, Y. Shen, W. B. Smith, O. Fedorov, E. M. Morse, T. Keates, T. T. Hickman, I. Felletar, M. Philpott, S. Munro, M. R. McKeown, Y. Wang, A. L. Christie, N. West, M. J. Cameron, B. Schwartz, T. D. Heightman, N. La Thangue, C. A. French, O. Wiest, A. L. Kung, S. Knapp and J. E. Bradner, *Nature*, 2010, **468**, 1067–1073.

233 C. Chung and J. Witherington, *SLAS Discov.*, 2011, **16**, 1170–1185.

234 J. Gavenonis, B. A. Sheneman, T. R. Siegert, M. R. Eshelman and J. A. Kritzer, *Nat. Chem. Biol.*, 2014, **10**, 716–722.

235 J. A. Wells and C. L. McClendon, *Nature*, 2007, **450**, 1001–1009.

236 L. Lombardi, L. A. Granger, R. J. Shattock and D. R. Williams, *J. Org. Chem.*, 2025, **90**, 1467–1477.

237 M.-C. Lu, Q. Jiao, T. Liu, S.-J. Tan, H.-S. Zhou, Q.-D. You and Z.-Y. Jiang, *Eur. J. Med. Chem.*, 2018, **143**, 1578–1589.

238 P. Furet, B. Salem, Y. Mesrouze, T. Schmelzle, I. Lewis, J. Kallen and P. Chène, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 2316–2319.

239 D. Marcotte, W. Zeng, J.-C. Hus, A. McKenzie, C. Hession, P. Jin, C. Bergeron, A. Lugovskoy, I. Enyedy, H. Cuervo, D. Wang, C. Atmanene, D. Roecklin, M. Vecchi, V. Vivat, J. Kraemer, D. Winkler, V. Hong, J. Chao, M. Lukashev and L. Silvian, *Bioorg. Med. Chem.*, 2013, **21**, 4011–4019.

240 S. Kaseda, Y. Sannomiya, J. Horizono, J. Kuwazuru, M. A. Suico, S. Ogi, R. Sasaki, H. Sunamoto, H. Fukiya, H. Nishiyama, M. Kamura, S. Niinou, Y. Koyama, F. Nara, T. Shuto, K. Onuma and H. Kai, *Kidney360*, 2021, **3**, 687–699.

241 M.-C. Lu, X. Zhang, F. Wu, S.-J. Tan, J. Zhao, Q.-D. You and Z.-Y. Jiang, *J. Med. Chem.*, 2019, **62**, 6796–6813.

242 D. A. Abed, A. R. Ali, S. Lee, M.-U. Nguyen, M. P. Verzi and L. Hu, *Eur. J. Med. Chem.*, 2023, **252**, 115302.

243 S. Lee, D. A. Abed, M.-U. Nguyen, M. P. Verzi and L. Hu, *Eur. J. Med. Chem.*, 2022, **237**, 114380.

244 X. Zhang, K. Cui, X. Wang, Y. Tong, C. Liu, Y. Zhu, Q. You, Z. Jiang and X. Guo, *Antioxidants*, 2023, **12**, 1062.

245 D. Narayanan, K. T. Tran, J. S. Pallesen, S. M. Ø. Solbak, Y. Qin, E. Mukminova, M. Luchini, K. O. Vasilyeva, D. González Chichón, G. Goutsiou, C. Poulsen, N. Haapanen, G. M. Popowicz, M. Sattler, D. Olagnier, M. Gajhede and A. Bach, *J. Med. Chem.*, 2022, **65**, 14481–14526.

246 G. H. S. Dreiman, M. Bictash, P. V. Fish, L. Griffin and F. Svensson, *SLAS Discov.*, 2021, **26**, 257–262.

247 T. Zhu, S. Cao, P.-C. Su, R. Patel, D. Shah, H. B. Chokshi, R. Szukala, M. E. Johnson and K. E. Hevener, *J. Med. Chem.*, 2013, **56**, 6560–6572.

248 G. N. Sundell and Y. Ivarsson, *Biomed. Res. Int.*, 2014, **2014**, 176172.

249 H. Wang and R. Liu, *Expert Rev. Proteom.*, 2011, **8**, 335–346.

250 J. Pei, J. Zhang and Q. Cong, *J. Mol. Biol.*, 2026, **438**, 169636.

This journal is © The Royal Society of Chemistry 2026