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Recent Advances in CBP/EP300 Degraders

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Abstract: Targeted protein degradation (TPD) has emerged as an innovative therapeutic strategy, offering advantage over traditional approaches rooted in small-molecule inhibitors. Among the various modalities in TPD, proteolysis targeting chimeras (PROTACs) and molecular glue degraders (MGDs) have arisen as leading modalities, distinguished by their ability to induce protein degradation *via* the ubiquitin-proteasome system (UPS). In recent years, extensive research has focused on developing degraders targeting CREB-binding protein (CBP) and E1A-associated protein (EP300) – two homologous multidomain enzymes critical for enhancer-mediated transcription. This review explores the state of the art in CBP/EP300 degraders, underscoring the significant potential of these synthetic bifunctional compounds as innovative chemical tools and highly promising anticancer agents.

Keywords: CBP · Degrader · EP300 · PROTAC

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Cristina Nevado received her PhD in 2004 from the Autónoma University (Madrid) working with Prof. Antonio M. Echavarren. After a postdoctoral stay in the group of Prof. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung (Germany) she started her independent career as an Assistant Professor of Organic Chemistry at the University of Zürich in 2007. In 2012 she received an ERC Junior Investigator grant and in 2013 was awarded the Werner Prize of the Swiss Chemical Society and was directly promoted to Full Professor. In 2019, she received the Royal Society of Chemistry Award in Organometallic Chemistry and in 2020 the Excellence Research Trajectory Award of the Royal Spanish Chemical Society (RSEQ) as well as the Margaret Faul Women in Chemistry Award in 2021. Among her many contributing roles to the community, Cristina has served as Senior Associate Editor for ACS Central Science, Organic Syntheses and now Science of Synthesis. Rooted in the wide area of organic chemistry, her research program is at the interface of complex chemical synthesis, new organometallic reactions and medicinal chemistry.

1. Introduction

1.1 *PROTACs and Molecular Glue Degraders*

In recent years, new therapeutic modalities based on targeted protein degradation (TPD)[1] have emerged, harnessing a cell's intrinsic protein degradation machinery such as the ubiquitin-proteasome system (UPS) and the lysosome.[2] Specifically, TPD modalities that exploit the UPS to drive protein degradation, such as proteolysis targeting chimeras (PROTACs)[3] and molecular glue degraders (MGDs),[4] have seen major developments both in academic and industrial settings.[5]

PROTACs are heterobifunctional molecules that consist of a binder for a protein of interest (POI) connected to an E3 ligase ligand *via* a suitable linker. Simultaneous binding of the POI and E3 ligase by a PROTAC brings the two proteins into close proximity, forming a so-called 'ternary complex' which results in the polyubiquitination and subsequent proteasomal degradation of the POI.[3] The mechanism of action of PROTACs is intrinsically different from that of small molecule inhibitors, which rely on the stoichiometric occupation of an active or allosteric site on an enzyme to shut down the function of the POI (occupancy-driven pharmacology). In contrast, PROTACs only need a transient binding event to recruit the E3 ligase and elicit their pharmacologic effect (protein degradation) in a catalytic manner (event-driven pharmacology).[6] PROTAC's mode of action bears the potential to lower the required effective dose, thereby reducing toxicity and offering a solution for emerging drug resistance. Furthermore,

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PROTACs allow targeting proteins previously defined as undruggable. Specifically, the activity of protein domains for which small inhibitors could not be developed can be blocked with PROTACs, by binding any other domain and inducing the degradation of the entire protein. Interestingly, PROTACs often show enhanced selectivity compared to the small molecule inhibitors from which they derive. Several PROTACs, derived from pan-inhibitors or ligands binding to homologous proteins, have been reported to selectively degrade a single protein target.[7] Indeed, PROTAC selectivity not only relies on the interaction of the ligand with the POI's binding pocket, but also on protein-protein interactions between the E3 ligase and the POI, which represent a much wider surface for specific chemical interactions. Additionally, as targeted degradation not only depends on ternary complex formation but on the following ubiquitination, the accessibility of the ubiquitin ligase to lysine residues in protein regions distant from the binding pocket may differ within paralogues, and lead to improved selectivity.[8] The promising advantages of PROTACs for clinical use have propelled the field into a period of rapid development, paving the way for a new direction in the pharmaceutical industry.[5]

In contrast, molecular glues degraders (MGDs) are monovalent small molecules that bind the POI, or more frequently, the E3 ligase, imparting structural changes to the protein surface that promote interactions with new protein substrates (neosubstrates).[4] Therefore, molecular glues promote the interactions between an E3 ligase and a neosubstrate (*i.e.* the POI) resulting in UPS degradation of the latter. The ability of MG-bound proteins to recognise structural motifs,[9] allows them to engage targets based on structural complementarity rather than ligand binding, enabling degradation of previously undruggable proteins. MGDs generally have a lower molecular weight and better chemical properties than PROTACs, providing an easier starting point for medicinal chemistry optimisation and clinical applications.

The critical challenge with MGDs is the discovery of initial molecules beyond the well-established Cereblon/thalidomide systems. In recent years, MGD screening methods have evolved from serendipitous discoveries to intentional strategies that integrate a range of approaches.[4a–c] Some of these are based on, target- and E3-agnostic strategies and employ unbiased screening methods – such as phenotypic assays and data mining – to discover MGDs without preselecting a specific target or E3 ligase. Other methods focus on a predetermined POI and/or E3 ligase and seek compounds that promote degradation of the target protein and/or exploit the chosen E3 ligase. Building on these advances, Schreiber and coworkers recently reported an innovative and rational MGD screening approach,[4d] relying on a DNA-encoded library to identify molecular glues that enhance cooperative protein–protein interactions.

1.2 *Other TPD Modalities*

Progress in small molecule-based hijacking of the UPS has inspired the development of other bifunctional molecules that leverage proximity-based approaches to degrade proteins. These include chimeras recruiting components of the E3 ligase complex other than the substrate receptor, such as E2 enzymes or different adaptor proteins.[10] In addition, the TPD field is further expanding to degrade proteins or organelles that cannot be engaged by the UPS. These novel approaches include LYTACs (lysosome-targeting chimeras), antibodies modified with a lysosome-targeting ligand,[11] which enable the internalisation and lysosomal degradation of a cell-surface protein target. Another approach involves technologies that rely on the use of autophagy (AUTACs, autophagy targeting chimeras)[12] and autophagosomes (ATTECs, autophagosome targeting chimeras).[13] AUTACs consist of a guanine derivative linked to the target ligand that induce autophagic clearance of intracellular protein or fragmented mitochondria. On the other hand, ATTECs bear a ligand to the autophagosome precursor protein LC3 connected to a binder of the target of interest and induce the incorporation of target intracellular proteins and lipids in autophagosomes and their subsequent degradation.

Given the growing significance and rapid expansion of TPD and its diverse approaches, numerous reviews have been published in recent years.[1,3,4a-c,10,14] This review aims to provide an overview of the latest advances in the development of PROTACs and MGDs specifically targeting CREB-binding protein (CBP) and E1A-associated protein (EP300).

2. CBP/EP300

2.1 *Structure and Function*

CBP or CREBBP and its paralogue EP300 or p300 are large (~300 kDa) and nearly ubiquitously expressed proteins featuring at least nine distinct functional domains (Fig. 1). These proteins share 58% identity at a full-sequence level, reaching a sequence identity of 97% in their bromodomain (BRD), which binds to acetylated lysine residues, and 88% in their histone acetyltransferase (HAT) catalytic domain, responsible for acetylating histones and other proteins.[15] Despite their similarity, peptide binding assays indicate that CBP and EP300 have different binding preferences within acetylated histones.[16]

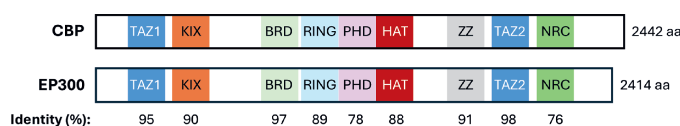

Fig. 1. Structural organisation of CBP and EP300 and aminoacidic sequence identity (%) of each domain. Domains are depicted with different colours, white indicates disordered regions.

Due to their multidomain (and multifunction) nature, CBP and EP300 interact with more than 400 protein partners - including histones, transcription factors, and chromatin regulators - making them crucial components of the protein-protein interactome.[17] They also interact with replication and repair proteins, playing significant roles in cell growth regulation and gene control through various signalling pathways.[18] Furthermore, genome-wide studies have shown that these proteins bind to active gene regions with high levels of acetylated histones, as well as to repressed gene regions with low acetylation levels, suggesting a role in chromatin remodelling,[19] and in the activation of enhancer-mediated transcription.[20,21] While originally described as histone acetyltransferases, CBP and EP300 are now understood to acetylate *ca.* 21,000 lysine residues on over 5,000 proteins.[22] These proteins are located primarily in the nucleus (such as histones) but are also present in other parts of the cell. However, it is not completely understood how they shuttle in and out of the nucleus and the influence that their binding partners have on this process.[21b]

Various studies have suggested that EP300 and CBP play overlapping but distinct roles in the regulation of cell survival. For example, mouse knockout experiments of either CBP or EP300 result in embryonic lethality with different phenotypes.[23] Furthermore, while CBP is required for self-renewal of hematopoietic stem cells, EP300 is essential for their differentiation.[24] In addition, several studies have identified largely overlapping but distinct binding of EP300 and CBP genome-wide, indicating that they regulate the enhancers of distinct genes.[25] However, many studies interrogating EP300 and CBP have relied on the use of inhibitors binding both enzymes.[26] Thus, the high homology of CBP and EP300 and the consequent lack of paralogue-selective inhibitors has limited the possibilities of independently elucidating the mechanisms regulated by each protein in cells.

2.2 *Implication in Disease*

The complex roles of CBP and EP300 are further highlighted by their dual functions as both oncogenes and tumour suppressors. Genetic mutations involving CBP or EP300, have been reported in leukaemia and lymphomas,[27] while their tumour suppressor activity is suggested by observations such as increased incidence of blood-related tumours in patients with Rubinstein-Taybi syndrome who have germline mutations in these genes.[28] Interestingly, Qui and coworkers have demonstrated that CBP has a limited role in the majority of high-risk paediatric neuroblastomas, which rather depend on enhancer acetylation by EP300 and its interaction with the TFAP2β transcription factor.[29]

Over the last twenty years, many efforts have focused on developing ligands for CBP/EP300. The chemical probe C646 has been used by many groups to study CBP/EP300 acetyltransferase activity *in cellulo*, but its utility is limited by clear off-target effects.[30] Later, HAT inhibitors with improved potency and selectivity have been developed and used to validate *in vivo* inhibition of CBP/EP300 catalytic activity as a promising cancer therapeutic strategy.[26e,31] In addition, following the therapeutic success of bromodomain and extra-terminal domain (BET) inhibitors and the significant binding of many non-selective BET inhibitors to CBP and EP300, there has been increasing interest in targeting their bromodomains, and several potent and selective bromodomain inhibitors have been described.[26d,32] However, evidence indicates that inhibiting either the bromo- or HAT domains of CBP/EP300 leads to distinct effects on lysine acetylation patterns and chromatin structure. HAT inhibitors tend to mimic the decrease in acetylation observed in CBP/EP300 genetic knockout models. Similarly, BRD inhibitors also reduce lysine acetylation of known CBP/EP300 targets, though to a lesser extent, as bromodomains serve for binding of several substrates to be acetylated.[22c] Notably, it was demonstrated that treatment of prostate cancer cells with a combination of CBP/EP300 BRD and HAT inhibitors led to synergistic antiproliferative activity, suggesting that this combined treatment reduces association of CBP/EP300 with chromatin compared to single-compound treatment.[33]

3. CBP/EP300 Inhibitors

Over the past decade, numerous potent CBP/EP300 inhibitors with therapeutical potential have been reported and the field has been reviewed.[34] The following section will focus exclusively on CBP/EP300 BRD (Fig. 2) and HAT (Fig. 3) inhibitors that have been used for the development of CBP/EP300 degraders. All inhibitors discussed here have been crystallised in complex with the BRD or HAT domain of CBP and/or EP300. The structural, pharmacological, and toxicological data collected during these studies have provided a foundation for the development of the corresponding PROTACs.

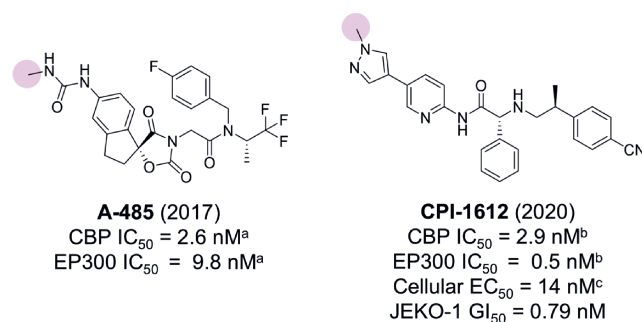

Fig. 3. Chemical structures of selected CBP/EP300 HAT inhibitors and their key properties. Reported *in vitro* IC_{50} measured by [a]TR-FRET or [b]SPA. [c]Cellular inhibition of H3K18 acetylation. Vectors used for PROTAC development are highlighted in pink.

3.1 *CBP/EP300 Bromodomain Inhibitors*

3.1.1 *GNE-049, GNE-781 and GNE-207*

In 2017 scientists at Genentech used structure-based design to develop GNE-049, a CBP/EP300 BRD inhibitor with excellent potency (CBP IC_{50} = 1.4 nM, EP300 IC_{50} = 2.3 nM, measured by TR-FRET).[32c] GNE-049 also showed excellent cellular potency in a Bioluminescence Resonance Energy Transfer (BRET) assay (CBP IC_{50} = 12 nM), and was shown to inhibit the expression of *MYC* (an oncogene regulated by CBP/EP300[35]) with an EC_{50} of 14 nM. In addition, GNE-049 was demonstrated to inhibit the growth of prostate cancer models both *in vitro* and *in vivo*, revealing a critical role for the CBP/EP300 bromodomain in regulating androgen receptor gene expression.[36] However, GNE-049 resulted in several central nervous system (CNS)-related adverse effects in mice. In pursuit of a more drug-like inhibitor, the authors set out to develop a molecule with increased total polar surface area and an additional hydrogen bond donor by replacing the acetamide acetyl-lysine KAc mimic of GNE-049 with a methyl urea. This led to GNE-781, a CBP/EP300 BRD inhibitor with improved *in vitro* (CBP IC_{50} = 0.94 nM, EP300 IC_{50} = 1.2 nM, TR-FRET)[32c] and cellular (IC_{50} = 6.2 nM, BRET) potency devoid of CNS adverse effects.[32c] GNE-781 inhibited the expression of *MYC* (EC_{50} = 6.6 nM) and showed antitumor activity in an acute myeloid leukaemia model. In addition, the inhibitor impaired the expression of forkhead box P3 (FOXP3), a transcription factor essential for immune response, in a dose-dependent manner, highlighting the potential of inhibiting CBP/EP300 bromodomain for cancer immunotherapy.

One year later, the same authors reported another study, focused on replacing the aniline present in the published GNE-049 series, as the oxidation of anilines can potentially produce toxic metabolites.[37] Among the reported compounds, the best

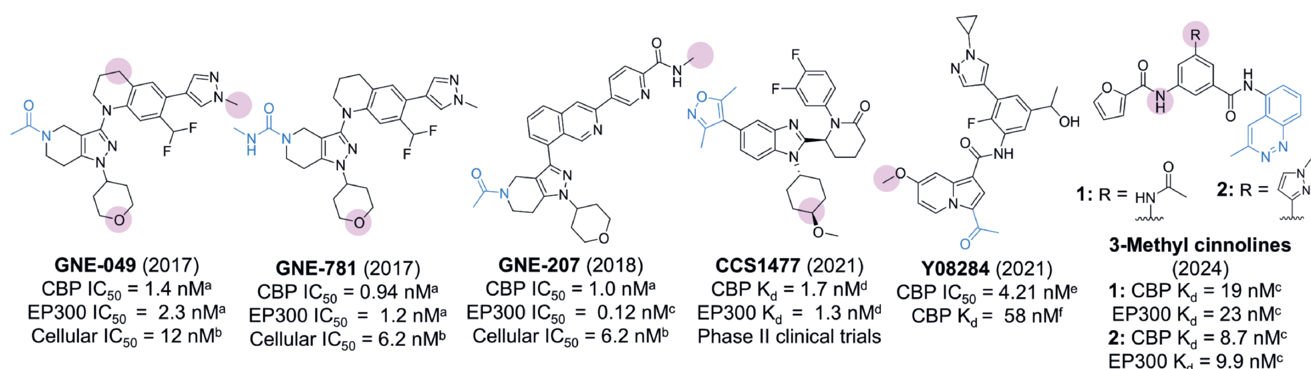

Fig. 2. Chemical structures of selected CBP/EP300 BRD inhibitors and their IC_{50} or K_d values measured by [a]TR-FRET, [b]BRET, [c]BROMOscan, [d]SPR, [e]HTRF or [f]ITC. Acetyl-lysine mimics are coloured in blue and vectors used for PROTAC development are highlighted in pink.

inhibitor, GNE-207, featured a quinoline-pyridine conjugated system, which showed comparable binding affinity (CBP IC_{50} = 1.0 nM) and *MYC* expression inhibition (EC_{50} = 18 nM) to GNE-049.

3.1.2 *CCS1477*

In 2021, De bono and coworkers reported a novel orally bioavailable CBP/EP300 BRD inhibitor, CCS1477[38] (CBP K_d = 1.7 nM , EP300 K_d = 1.3 nM, measured by Surface Plasmon Resonance, SPR), though information on its optimisation and binding pose was not disclosed. The crystal structures of CCS1477 in complex with the bromodomain of EP300 and CBP were reported later by the Xiang[39] and Durbin groups,[40] elucidating the binding mode of the inhibitor and showing the dimethyl isoxazole acts as a KAc mimic. CSS1477 was demonstrated to inhibit the growth of Androgen Receptor (AR)-positive cancers in a dose-dependant manner, by decreasing AR and *MYC* gene expression and exhibited antitumour activity in a mouse model. CCS1477 is the first CBP/EP300 inhibitor to enter clinical testing and is currently in phase II clinical trials for the treatment of prostate cancer.

3.1.3 *Y08284*

Xu and coworkers reported in 2021 the structural optimisation of a series of CBP bromodomain inhibitors based on a 1-(indolizin-3-yl)ethan-1-one scaffold.[41] These ligands effectively inhibited the CBP bromodomain with nanomolar IC_{50} values and exhibited high selectivity over other members of the bromodomain family. Among the most promising compounds, Y08284 showed potent inhibition of the CBP bromodomain protein, with an IC_{50} value of 4.21 nM, and effectively suppressed the proliferation of prostate cancer cell lines LNCaP, C4-2B, and 22Rv1. Additionally, Y08284 inhibited androgen receptor (AR)-mediated gene expression in a dose-dependent manner, reducing AR protein expression. The compound demonstrated favourable cell permeability, good pharmacokinetic properties, and an oral bioavailability of 25.9%. Moreover, Y08284 exhibited significant antitumor efficacy *in vivo* in a 22Rv1 xenograft mouse model.

3.1.4 *3-Methyl Cinnoline Derivatives*

In 2024, Nevado, Caflisch and coworkers reported CBP/EP300 inhibitors featuring 3-methyl cinnoline as an unprecedented acetyl-lysine mimic.[42] From an *in silico* screening of a library of about 500 small molecules, the 3-methylcinnoline scaffold was discovered by high-throughput fragment docking using the program SEED.[43] Using a fragment-growing strategy based on the visual analysis of the overlap between the docked pose of 3-methylcinnoline in the CBP bromodomain and the crystal structure of a previously reported acetophenone-based ligand,[44] the authors replaced the acetophenone group with 3-methylcinnoline to obtain CBP/EP300-BRD inhibitor **1** (Fig. 2). Subsequent optimisation for *in cellulo* and *in vivo* applications led to the development of compound **2**.[42]

3.2 *CBP/EP300 HAT Inhibitors*

3.2.1 *A-485*

In 2017, researchers at AbbVie reported A-485, a selective inhibitor of the CBP/EP300 HAT domain.[26e] Its development started from a virtual screening based on docking of bi-substrate (lysine/acetyl-CoA) analogues. Through structure-based optimisation, A-485 was refined to selectively inhibit CBP/EP300 (CBP IC_{50} = 2.6 nM, EP300 IC_{50} = 9.8 nM, measured by TR-FRET) by occupying the acetyl-CoA binding site without interfering with the peptide binding site. The authors assessed the ability of A-485 to inhibit proliferation across 124 cancer cell lines, demonstrating strong efficacy in haematological and AR-positive tumour cell lines. Further investigation in a castration-resistant prostate cancer model revealed that A-485 also inhibited tumour growth *in vivo*.

3.2.2 *CPI-1612*

In 2020, Levell and coworkers reported CPI-1612, a potent and orally bioavailable CBP/EP300 HAT inhibitor.[31b] CPI-1612, was developed by structure-based optimisation of a hit compound identified *via* high-throughput screening.[45] Structural data revealed that the compound is occupying the acetyl-CoA binding site, while an *in vitro* Scintillation Proximity Assay (SPA) demonstrated that CPI-1612 inhibits full-length CBP and EP300 with IC_{50} values of 2.9 and 0.5 nM, respectively. CPI-1612 also inhibited histone 3 acetylation at lysine 18 (H3K18Ac) *in cellulo* with an EC_{50} = 14 nM and suppressed the growth of JEKO-1 cancer cells with GI_{50} of 0.79 nM. The inhibitor has good pharmacokinetic profiles in mice and dogs, but not in rats, and is devoid of any significant off-target activity. Moreover, CPI-1612 suppressed histone acetylation at the primary chromatin acetylation sites of CBP/300 *in vivo* in a dose-dependent manner and was able to inhibit tumour growth in a mantle cell lymphoma mouse model.

4. CBP/EP300 PROTACs

Given the distinct roles of CBP/EP300 domains in regulating gene expression and the synergistic antiproliferative activity demonstrated by simultaneous inhibition of the HAT and BRD domains in prostate cancer,[33] chemical knockdown of the whole proteins – *e.g.* by PROTACs – may bring therapeutic advantages. The growing interest in the development of CBP/EP300 degraders is reflected by the substantial number of PROTACs reported in recent years. This section provides a chronological overview of the CBP/EP300 PROTACs reported to date.

4.1 *dCBP-1*

The first CBP/EP300 PROTAC, dCBP-1, was reported by Ott and coworkers in 2021 (Fig. 4A).[46] dCBP-1 is based on the CBP/EP300 inhibitor GNE-781[32c] and the morpholine ring was used as a vector for the attachment of the thalidomide CRBN ligand through a PEG4 linker. dCBP-1 induces nearly complete degradation of both CBP and EP300 within 2 hours of treatment in the HAP1 cells and in several myeloma cell lines. dCBP-1 was able to decrease the viability of a panel of 21 myeloma cell lines to a greater extent than pomalidomide or the BRD and HAT inhibitors GNE-781 and A-485,[26e] and also downregulated the oncogene *MYC*. Later, the Ott group explored other vectors of GNE-781 (*i.e.* pyrazole and tetrahydroquinoline) for developing CBP/EP300 PROTACs by investigating the structure-activity relationship of a small set of dCBP-1 analogues.[47]

4.2 *JQAD1*

In 2022, Qi and coworkers reported the first PROTAC, JQAD1 (Fig. 4A), based on a CBP/EP300 HAT inhibitor,[26e] and able to, at least to an extent, selectively degrade EP300 in multiple neuroblastoma (NB) cell lines and in mice with limited toxicity.[29] However, the PROTAC degrades EP300 only after 16-24 hours, and CBP loss also starts to occur after 48 hours. JQAD1 induces apoptosis in NB cells, downregulates the expression of the *MYCN* oncogene at a transcriptional level, and, in some cell lines, exhibits a higher antiproliferative effect than its parent inhibitor, A-485. However, neither the degradation nor the selectivity reported by JQAD1 in NB could be mimicked in other cell lines.[48,49]

4.3 *JET-209*

Notably, an exceptionally potent CBP/EP300 degrader, JET-209, was reported by the Wang group in 2023 (Fig. 4A).[50] JET-209 is based on the GNE-207 bromodomain inhibitor[37] and degrades CBP/EP300 with DC_{50} values of 0.1 and 0.2 nM in the

RS4;11 leukaemia cell line after a 4 hour treatment. JET-209 has strong antiproliferative effects: it outperforms dCBP1 and JQAD1 in RS4;11 cells and CBP/EP300 BRD and HAT inhibitors in several leukaemia cell lines. JET-209 downregulates the expression of *MYC* and *MYB* oncogenes, it is able to degrade CBP/EP300 *in vivo* and it can inhibit tumour growth in a xenograft mouse model.

4.4 *dCE-1*

In January 2024, the Nevado group reported a CBP/EP300 PROTAC named dCE-1[48] (Fig. 4B, top left), consisting of the HAT inhibitor CPI-1612 conjugated *via* a 24-atom linker to pomalidomide. dCE-1 is a degrader of CBP/EP300 with a DC_{50} = 1.3 µM in the human myeloma LP1 cells. Notably, in this work, *in cellulo* ternary complex formation was determined for the first time for CBP PROTACs using fluorescent-based technology detecting protein−protein interactions (FluoPPI) with an EC_{50} = 1.2 µM. The application of FluoPPI in the discovery of dCE-1 shed light on the reasons for PROTAC performance and aided in the exploration of PROTAC-SAR.

4.5 *QC-182*

In February 2024, Li and coworkers reported QC-182 (Fig. 4B, top right), a PROTAC characterised by the BRD inhibitor CCS1477 connected *via* a 'minimalistic' azetidine linker to thalidomide.[51] QC-182 degrades EP300 with a DC_{50} = 93 nM in SK-HEP-1 hepatocellular carcinoma cells, though dose-response degradation for CBP was not measured. Furthermore, QC-182 was more effective than its parent inhibitor (CCS1477) and the reported degrader dCBP-1 in inhibiting cell growth of two different hepatocellular carcinoma cell lines (SK-HEP-1 and JHH-7), and depleted CBP/EP300 in a mouse model.

4.6 *CBPD-268 and CBPD-409*

In March 2024, the Wang group reported two orally bioavailable PROTACs, CBPD-268[52] (Fig. 4B, middle left) and CBPD-409[53] (Fig. 4B, middle), based on GNE-049 and thalidomide but with different (rigid) linkers. Both compounds are extremely potent degraders with picomolar DC_{50} values in three different AR-positive prostate cancer cell lines (CBP/EP300 DC_{50} ≤ 0.03 nM, D_{max} ≥ 98% for CBPD-268; CBP/EP300 DC_{50} ≤ 0.04 nM,

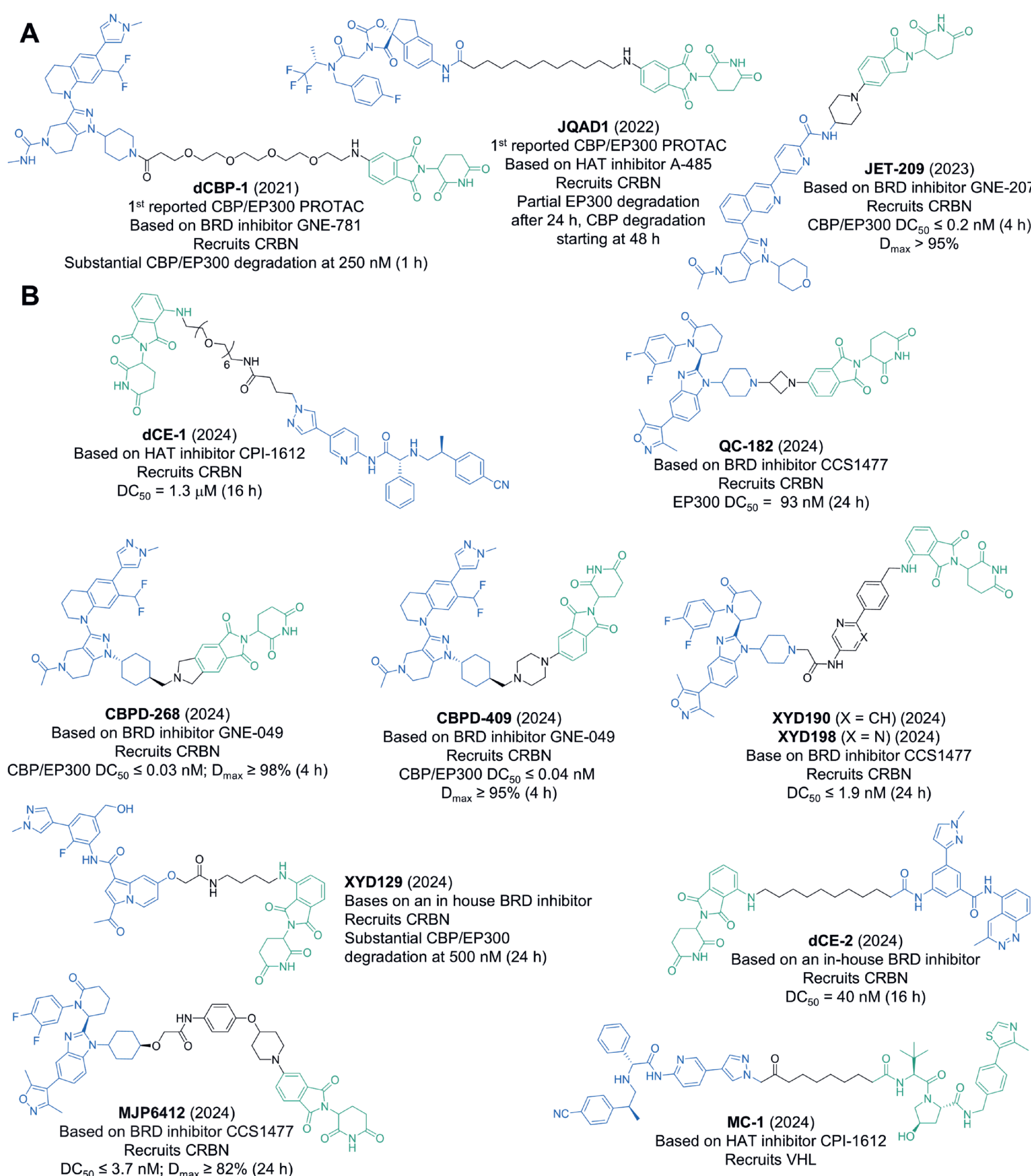

Fig. 4. A) CBP/EP300 PROTACs reported between 2021-2023. B) CBP/EP300 PROTACs reported in 2024. CBP/EP300 ligands are coloured in blue, E3 ligase binders in green and linkers in black.

D_{max} ≥ 95% for CBPD-409) and are able to achieve CBP/EP300 degradation *in vivo*.

4.7 *XDY190, XDY198 and XYD129*

In April 2024, Xu and coworkers reported the development of a series of CRBN-recruiting CBP/EP300 PROTACs derived from the inhibitor CCS1477, employing the same vector (*i.e.* cyclohexyl moiety) as in QC-182.[54] The lead compounds, XYD190 and XYD198 (Fig. 4B, middle-right), showed potent CBP/EP300 degradation (DC_{50} ≤ 1.9 nM) and inhibited the growth of acute myeloid leukaemia cells (IC_{50} ≤ 1.8 nM). Both compounds also demonstrated a greater ability to reduce *in vivo* tumour growth compared to CCS1477. Shortly after, the same group reported a new series of degraders,[55] obtained by conjugating the CBP/EP300 bromodomain inhibitor Y08284[41] to pomalidomide. The most promising compound, XYD129 (Fig. 4B, middle-left), induced substantial degradation of CBP/EP300 at 500 nM after 24 hours and inhibited the growth of MOLM-16 cells to a greater extent than its parent inhibitor, though it was less effective than CCS1477. XYD129 also suppressed tumour growth in a mouse model, albeit its effects were not compared to any CBP/EP300 bromodomain inhibitor or degrader. Despite being based on an in-house inhibitor, XYD129 is evidently a less efficient degrader than other PROTACs derived from more potent small molecules.

4.8 *dCE-2*

In August 2024, Nevado, Caflisch and coworkers reported dCE-2,[56] a structurally novel CBP/EP300 PROTAC based on a 3-methylcinnoline derivative conjugated to a thalidomide CRBN E3 ligand *via* a 10-atom aliphatic linker (Fig. 4B, middle-right). The design of dCE-2 was based on the crystal structure of an in house BRD inhibitor (compound **1**, Fig. 2) featuring a 3-methylcinnoline acetyl-lysine mimic discovered by high-throughput fragment docking. dCE-2 is active across several cell lines (LP1, MM1S, LNCaP, and SH-SY5Y) with a DC_{50} = 40 nM after 16 h in LP1 cells. dCE-2 can form a ternary complex with CBP and CRBN both *in cellulo* (FluoPPI) and *in vitro* (TR-FRET) with high cooperativity (α = 3.4). Interestingly, despite the modest K_d values of dCE-2 toward CBP/EP300 bromodomains (CBP K_d = 1300 nM, EP300 K_d = >10,000 nM, as determined by BROMOscan technology) this PROTAC demonstrated highly efficient degradation of both proteins. This behaviour was rationalised using molecular dynamics (MD) simulations, which revealed that dCE-2 can switch between compact and extended conformations. This conformational flexibility may impair binding in biochemical assays but enhances cell permeability.

4.9 *MJP6412*

In September 2024, Qin and coworkers developed a CBP/EP300 PROTAC, MJP6412 (Fig. 4B, lower left), also derived from the inhibitor CCS1477.[57] The degrader is based on the same vector and CRBN binder as the compounds previously reported by the Li[51] and Xu[56] groups, and only differs in the nature of the linker. MJP6412, induced CBP/EP300 degradation at low nanomolar concentrations in the three different AR-positive prostate cancer cell lines (CBP DC_{50} = 1.2–3.7 nM, D_{max} = 82–89%; EP300 DC_{50} = 1.6–3.4 nM, D_{max} = 94–97%) and inhibited their growth more potently than CCS1477. Furthermore, MJP6412 reduced AR and *MYC* protein expression more efficiently than CCS1477, recapitulating the effects of CBP/EP300 bromodomain inhibition in prostate cancer. Moreover, *in vivo* studies showed that MJP6412 has acceptable pharmacokinetic properties and reduced tumour growth in a mouse model.

4.10 *MC-1*

In July 2024, Meier and coworkers reported a PROTAC, MC-1 (Fig. 4B, lower right), based on the derivatives of the HAT inhibitor CPI-1612 included in our work,[48] claiming selective degradation of EP300 over CBP.[49] However, MC-1 also degrades CBP at higher concentrations (EP300 D_{max} = 80%; CBP D_{max} = 40%), induces the formation of a ternary complex with VHL and both CBP and EP300, and competes with a CPI-1612 derivative for binding to both paralogues. When carefully analysed, these findings point towards a kinetic or concentration-dependent bias rather than selectivity for EP300 degradation.

5. CBP/EP300 Molecular Glue Degrader

In 2024, Wang and coworkers reported a series of molecular glues degrading CBP/EP300 by engagement of the RNF126 ubiquitin ligase.[58] These compounds are based on the GNE781 BRD inhibitor and JP-2-196, the covalent handle binding to the E3 ligase RNF126, discovered by the Nomura group and Novartis Pharma.[59] The most efficient degrader, compound A8 (Fig. 5), degrades CBP/EP300 in a time- and concentration-dependent manner, with DC_{50} values of 454 nM and 291 nM. A8 also inhibited proliferation of a panel of CBP/EP300-dependent cancer cell lines and showed a more profound effect than GNE272 in MV4-11 cells.

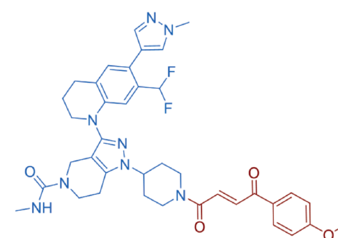

Fig. 5. Chemical structure of A8, a CBP/EP300 molecular glue degrader. The covalent handle binding the E3 ligase is coloured in red.

6. Conclusions

The number of CBP/EP300 PROTACs reported in recent years underscores the interest in degrading such disease-relevant enhancer factors, with the potential of preferentially targeting a single paralogue. Notably, most of these degraders demonstrate stronger phenotypic effects in cancer compared to their parent inhibitors, highlighting the therapeutic advantages of PROTACs and their utility in validating the roles of CBP and EP300 in disease. The vast majority of these PROTACs are based on thalidomide, which is known to have favourable physicochemical properties compared to other E3 ligase ligands. However, this reliance on thalidomide also reveals limitations for further clinical development, due to its known off-target effects and stability issues. In the coming years, we expect to see the development of more CBP/EP300 PROTACs with enhanced selectivity and safety profiles, paving the way for their potential clinical applications.

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Author Contributions

Conceptualization, L.P., I.C.-S. and C.N.; Writing original draft preparation, review and editing, L.P., I.C.-S. and C.N. All authors have read and agreed to the published version of the manuscript.

Abbreviation

Targeted protein degradation	TPD
Proteolysis targeting chimeras	PROTACs
Molecular glue degraders	MGDs
Ubiquitin-proteasome system	UPS
CREB-binding protein	CBP
cAMP response element-binding	CREB
Cyclic adenosine monophosphate	cAMP
E1A-associated protein	EP300
Adenovirus early region 1A	E1A
Protein of interest	POI
Lysosome-targeting chimeras	LYTACs
Autophagy targeting chimeras	AUTACs
Autophagosome targeting chimeras	ATTECs
Bromodomain	BRD
Histone acetyltransferase	HAT
Transcription factor activator protein 2β	TFAP2β
Microtubule-associated protein 1A/1B-light chain 3	LC3
Bromodomain and extraterminal domain	BET
Time-resolved fluorescence energy transfer	TR-FRET
Bioluminescence resonance energy transfer	BRET
Acetylated lysine	KAc
Forkhead box P3	FOXP3
Dissociation constant	K_d
Surface plasmon resonance	SPR
Androgen receptor	AR
Half maximal inhibitory concentration	IC_{50}
Homogeneous time resolved fluorescence	HTRF
Isothermal titration calorimetry	ITC
Lymph node carcinoma of the prostate	LNCaP
Scintillation proximity assay	SPA
Neuroblastoma	NB
Half-maximal degradation concentration	DC_{50}
Fluorescent-based technology detecting protein–protein interactions	FluoPPI
Structure–activity relationship	SAR
Cereblon	CRBN
Multiple myeloma	MM
Cooperativity	α
Molecular dynamics	MD
Von Hippel-Lindau	VHL
Ring finger protein 126	RNF126

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