Visualized Cancer Medicine 2022, **3**, 3
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https://doi.org/10.1051/vcm/2022004

Available online at:
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REVIEW ARTICLE OPEN ACCESS

CBP/p300 bromodomain: new promising epigenetic target

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Received 13 July 2022, Accepted 17 August 2022, Published online 11 September 2022

Abstract – CREB (cAMP responsive element binding protein) binding protein (CBP) and adenovirus E1A-associated 300 kDa protein (p300) are histone acetyltransferases, which are necessary for multiple cellular processes. Thus, CBP/p300 are promising potential antitumor targets. To date, despite various small molecule inhibitors of CBP/p300 bromodomain (BRD) having been reported, no specific inhibitor was approved by U.S. Food and Drug Administration (FDA). In this review, we described the discovery, optimization, binding mode evaluation, selectivity and potency evaluation, and therapeutic opportunities of our CBP/p300 bromodomain inhibitors, aiming to inspire new inhibitor design and advance drug discovery research in this field. One video presents the development of CBP/p300 bromodomain inhibitors.

Key words: CBP/p300, Bromodomain, Inhibitor, Prostate cancer.

Introduction

CREB (cAMP responsive element binding protein) binding protein (CBP) and p300 are lysine acetyl transferases that play a key role as transcriptional coactivators in cells [1–6]. CBP and p300 show high structural similarity and functional redundancy (Figure 1) [7, 8]. Several studies have shown that CBP and p300 (hereafter together referred to as "CBP") have been involved in masses of diverse biological functions including proliferation, cell cycle regulation, apoptosis, differentiation, and DNA damage response. Thus, overexpression or mutations of CBP have been implicated in several diseases, especially leukemia and prostate cancer [9–16].

CBP and p300 are large proteins with ~2400 amino acids and share ~75% sequence similarity (Figure 1) [11, 17, 18]. CBP and p300 consist of several highly conserved domains, including a catalytic histone acetyltransferase (HAT) domain that acetylates histones and other proteins, and an adjacent bromodomain that recognizes acetylated histone tails [19]. These two domains have been recognized as promising targets for antitumor treatment [20–22].

Bromodomains (BRDs) are named after the Drosophila gene Brahma where the BRD sequence motif was first identified in the early 1990s [23, 24]. Since then, BRDs have been identified in a variety of proteins, including transcriptional coactivators [25–27], methyltransferases [28, 29], and HATs [30]. Ten years later, Zeng and Zhou defined that BRD can specifically recognize the acetylated lysine (KAc) mark on histones [31]. BRDs are made up of approximately 110 amino acids. Regardless of the diversity in their sequence, BRDs share a conserved specialized structure that consists of four alpha-helices (αZ, αA, αB, and αC), linked by variable loop regions (ZA loop and BC loop), forming the largely hydrophobic KAc binding pocket (Figure 2A and Video 1) [32]. BRDs bind the KAc N-acetyl group via a hydrogen bond between the acetyl carbonyl and the NH_2 of a highly-conserved asparagine residue (Asn1168 in CBP) and a water-mediated hydrogen bond from the acetyl carbonyl to the phenolic hydroxyl group of a conserved tyrosine (Tyr1125 in CBP) [33, 34]. In addition, five conserved water molecules present at the bottom of the pocket have a significant impact on compound's binding affinity [35]. For CBP bromodomain, it should be kept in mind that small molecules gaining interactions to "LPF shelf" (Leu1109, Pro1110,

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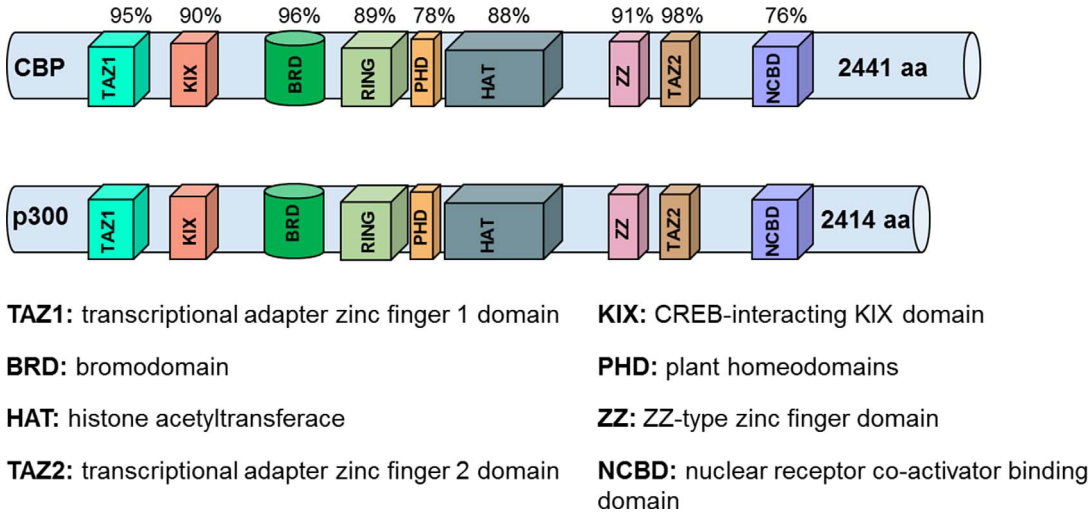


Figure 1. The domain structure and percent sequence identity of CBP and p300.

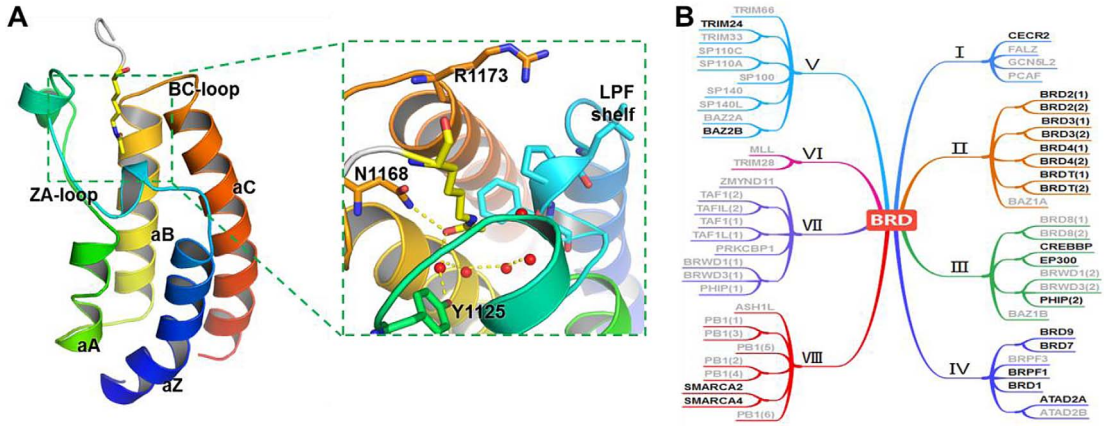
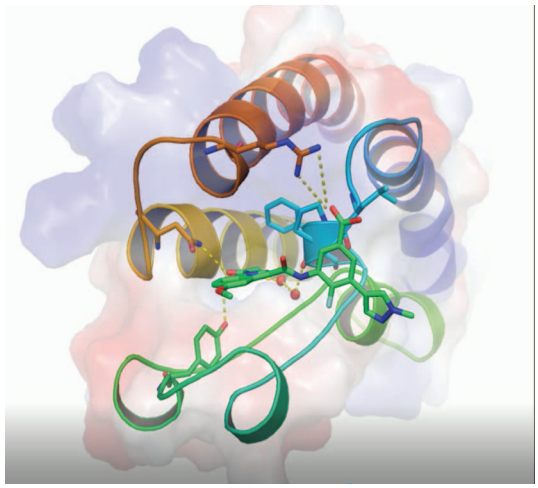


Figure 2. Bromodomain structure and phylogenetic tree. (A). Structure of an acetyl lysine and CBP bromodomain complex. CBP bromodomain-fold depicting the four α-helices (αZ, αA, αB, αC) and the endogenous ligand KAc (derived from PDB 5GH9). (B). Phylogenetic tree of the human bromodomain proteins.



Video 1. New scaffolds of CBP bromodomain inhibitors, a virtual screening strategy was used as shown. https://vcm.edpsciences.org/10.1051/vcm/2022004#V1.

Phe1111) and Arg1173 can be used to enhance potency and selectivity [36–39].

In the human proteome, there are 61 BRDs found in 46 different proteins [40] (Figure 2B). Moreover, based on sequence and structural similarity, human BRDs can be grouped into eight subfamilies with very different functions, and several of them have been implicated in human diseases, mainly cancer, and inflammation [41]. The bromodomain present in CBP, belongs to BRD family III. CBP has a single bromodomain along with several protein interaction motifs. They are associated with a number of biological functions and act as transcriptional coactivators [42].

In recent years, the development of CBP bromodomain inhibitors has attracted great attention from research institutions and major pharmaceutical companies due to their potential therapeutic value in the treatment of cancers and other diseases [36, 37, 39, 43–55]. Known small-molecule CBP bromodomain inhibitors mainly include 3,5-dimethylisoxazole (SGC-CBP30) [36], dihydroquinoxalinone (compound **2**) [43], benzoxazepine (I-CBP112) [55], benzodiazepinone (CPI-637) [47], and

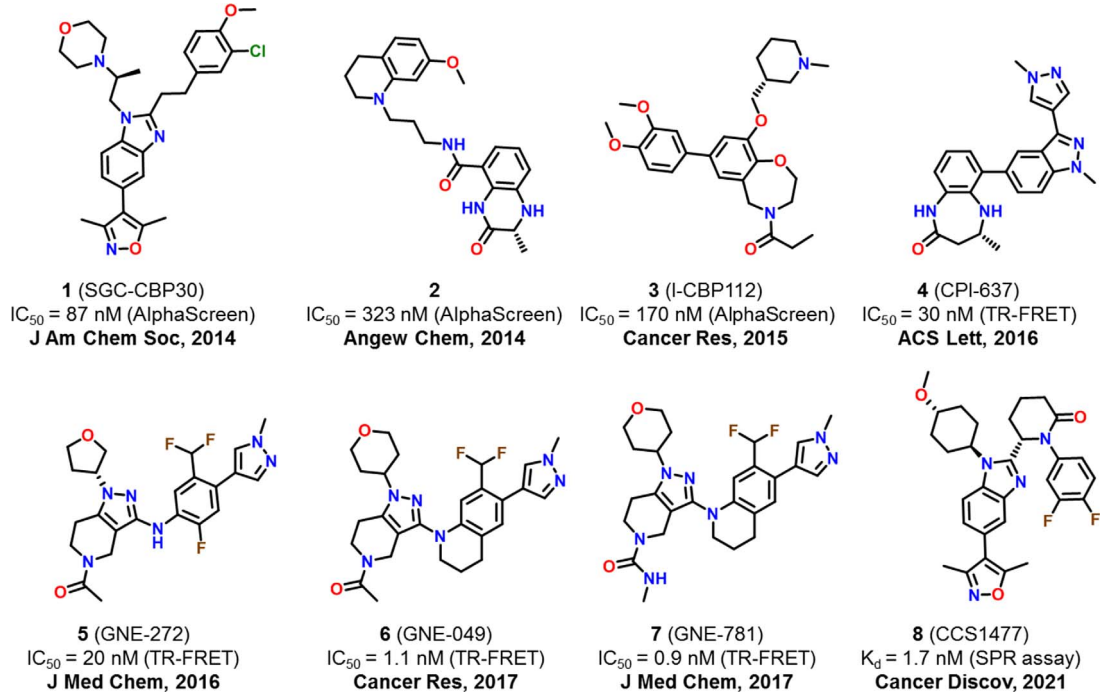


Figure 3. Structures of representative CBP bromodomain inhibitors.

pyrazolopiperidine (GEN-272 and GNE-781) [39, 45], etc. (Figure 3). The first potent inhibitor for CBP bromodomain was acetyl-lysine mimetic moiety based on 3,5-dimethylisoxazole, which was later optimized as SGC-CBP30 [36, 56]. Other CBP bromodomain probes, such as **2**, I-CBP112, and CPI-637, displayed good selectivity for CBP bromodomain over other bromodomains and showed significant inhibition in multiple tumor cells demonstrating the feasibility of targeting CBP bromodomain for cancer therapy. GNE-049 is a potent and selective CBP inhibitor developed by Genentech, which suppresses prostate cancer growth both in vitro and in vivo [16, 39]. CCS1477, developed by CellCentric, is the first CBP bromodomain inhibitor entering clinical trials. Recently, the phase I/IIa clinical trial was performed to evaluate its safety and pharmacokinetics in advanced drug-resistant prostate cancer and hematological tumors [53, 57]. However, there is no CBP bromodomain inhibitor approved by the U.S. Food and Drug Administration (FDA) to date. Therefore, it is an urgent need to discover novel, potent and specific CBP bromodomain inhibitors with different chemotypes to explore the full therapeutic potential of various human cancers.

In the first part of this review, we summarize the development of our CBP bromodomain inhibitors. The structure-activity relationship studies (SARs), binding models analysis, and biochemical evaluation are also addressed. In the second part, we discuss the opportunities and challenges as well as novel approaches and strategies in the generation of chemical tools and probes for CBP bromodomain. Hopefully, the perspective will provide new insights for pharmaceutical workers to develop more drug-like CBP inhibitors.

CBP bromodomain inhibitors

To obtain new scaffolds of CBP bromodomain inhibitors, a virtual screening strategy [58–61] was used as shown in Figure 4 shown in Video 1. First, the SPECS database was filtered [50]. Then, the resulting fragments were screened through molecular docking, cluster analysis, and visual inspection. At last, 13 representative compounds were selected and purchased for biological evaluation. Among them, compound **QP6** exhibited modest inhibitory activity against CBP with an IC_{50} value of 16.73 μM and exhibited good selectivity over other bromodomain-containing proteins. The molecular docking study indicated that compound **QP6** formed a critical hydrogen bonding with Asn1168, mimicking the acetylated lysine interaction observed between CBP and its substrate. In addition, the propionic acid group formed a hydrogen bond with Arg1173. Further optimization was performed based on compound **QP6**.

To ensure small molecule inhibitors can reach the LPF shelf and form further interactions with CBP, the propionic acid group was replaced with larger groups. Replacement of the propionic acid with a heterocyclic group yielded conformation constrained analog **QP45**, with a slight increase in inhibitory activity (IC_{50} = 6.8 μM). The cocrystal structure of the **QP45**/CBP bromodomain showed that **QP45** plugged into the narrow pocket with its 1-(1H-indol-3-yl)ethanone group interacting with the conserved residues Asn1168 and Tyr1125 (Figure 5). The 1-propionylpiperidine-3-carboxylic acid group protruded out of the pocket and reached the LPF shelf, forming further interactions with CBP. Moreover, the carboxyl group

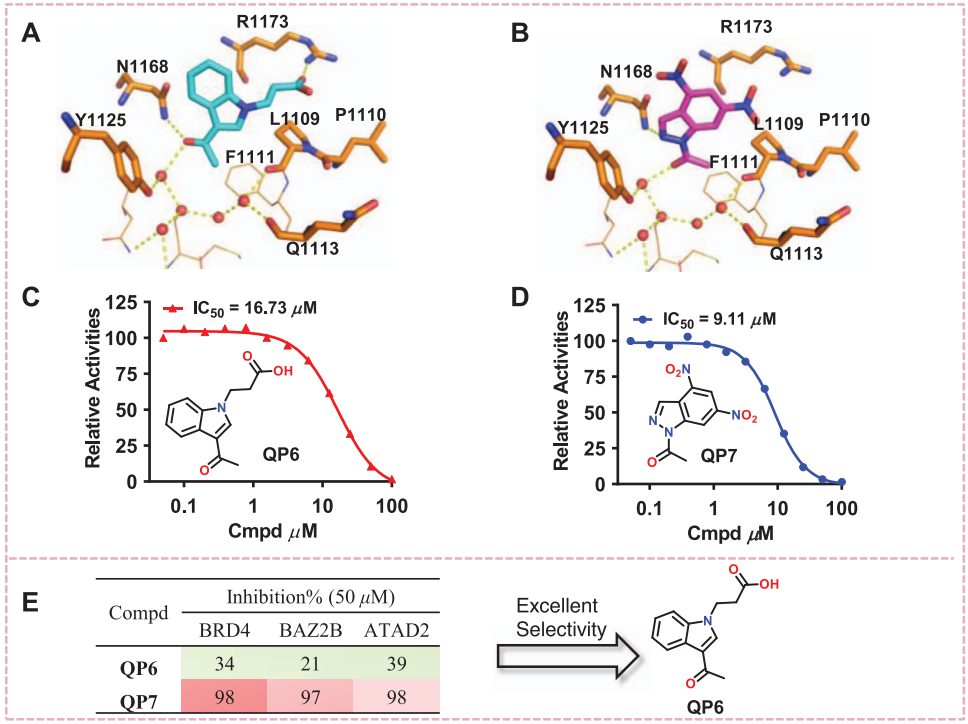


Figure 4. Experimental validation for compounds **QP6** and **QP7**. Predicted binding modes of **QP6** (A) and **QP7** (B) in complex with CBP protein. The inhibitory curves of **QP6** (C) and **QP7**. Half-maximum inhibitory concentration (IC_{50}) values for **QP6** (C) and **QP7** (D) in AlphaScreen assay. (E) Selectivity profile of **QP6** and **QP7**. Bromodomains' selectivity profiles were determined by AlphaScreen.

was involved in a canonical hydrogen bond with Arg1173. The crystal structure also revealed that the carbonyl of the 1-propionylpiperidine-3-carboxylic acid group interacts with Arg1173 through a water-mediated hydrogen bond. To obtain more potent compounds through water-mediated hydrogen bonds, the head group 1-(1H-indol-3-yl)ethanone was replaced with 1-(1H-indol-1-yl)ethanone with an amide linker attached, which afforded compound **QP82** with an IC_{50} value of 1.69 μM. This finding demonstrated that the carboxyl group of compound **QP82** was critical for binding activity.

Then, the SAR on the benzene ring was explored. The findings suggested that small groups at the ortho-position were favorable. For the meta-position, the furan group (**QP94**) is a favorable moiety to improve the activity (AlphaScreen IC_{50} = 0.65 μM). The predicted binding mode of **QP94** with CBP (Figure 5) indicated that there is some space near the BC channel and the C-6 position of the indole ring was explored. Hydroxyl (OH) and methoxy (OMe) groups indicted 4 times more potent than **QP94**, while longer linkers were found detrimental, likely due to the requirement of small size for the BC channel. To find a more effective CBP bromodomain inhibitor, the furan group was replaced by a 1-methyl-1-H-pyrazole motif, resulting in compound **QP175** as a potent CBP bromodomain inhibitor (AlphaScreen IC_{50} = 0.037 μM). However, its relatively low cellular potency and unsatisfactory metabolic stability limit its further development.

To improve metabolic stability, we replaced the 1-(1H-indol-1-yl)ethan-1-one in **QP175** with 1-(indolizin-3-yl)ethan-1-one, resulting in **QP180** (Figure 6A) [51, 54]. In comparison to **QP175**, compound **QP180** showed a significant potency improvement against CBP bromodomain with an IC_{50} value of 9.80 nM in the HTRF assay and 18-fold more potent than **QP175** (HTRF, IC_{50} = 178.15 nM). However, **QP180** did not show any cellular activity, which may be due to the limitation of cell permeability caused by highly polar carboxylic acid moiety. Therefore, further optimization was focused on improving cellular potency, leading to molecule **QP210** with favorable cellular activity (IC_{50} = 5 μM) in C4-2B cells. Unfortunately, **QP210** displayed poor oral bioavailability (F = 0.58%), which limited the use of this compound for in vivo evaluation. Further structural modifications were then conducted to improve the pharmacokinetic profiles of **QP210**. Thus, compound **QP268** was obtained and displayed promising pharmacokinetic properties. The compound exhibited a reasonable maximum concentration (C_{max} = 2037.80 μg/L), and acceptable half time ($t_{1/2}$ = 3.24 h). Unfortunately, it still showed poor oral bioavailability (F = 6.18%) in SD rats at an oral dose of 25 mg/kg.

The co-crystal structure of compound **QP268**-CBP bromodomain is consistent with our computational prediction (Figures 6B–6D). The acetyl group of **QP268** forms a hydrogen bond with the conserved residue Asn1168 and interacts with the conserved residue Tyr1125 through a water-mediated hydrogen bond. An additional hydrogen bond was also observed, the oxygen atom of the $-CH_2OH$ group formed a direct hydrogen bond with residue Leu1109. The X-ray structure analysis also revealed that the $-CH_2OH$ moiety of compound **QP268** was exposed to a partially opened hydrophobic pocket. It provides an ideal position for further structural optimization to improve

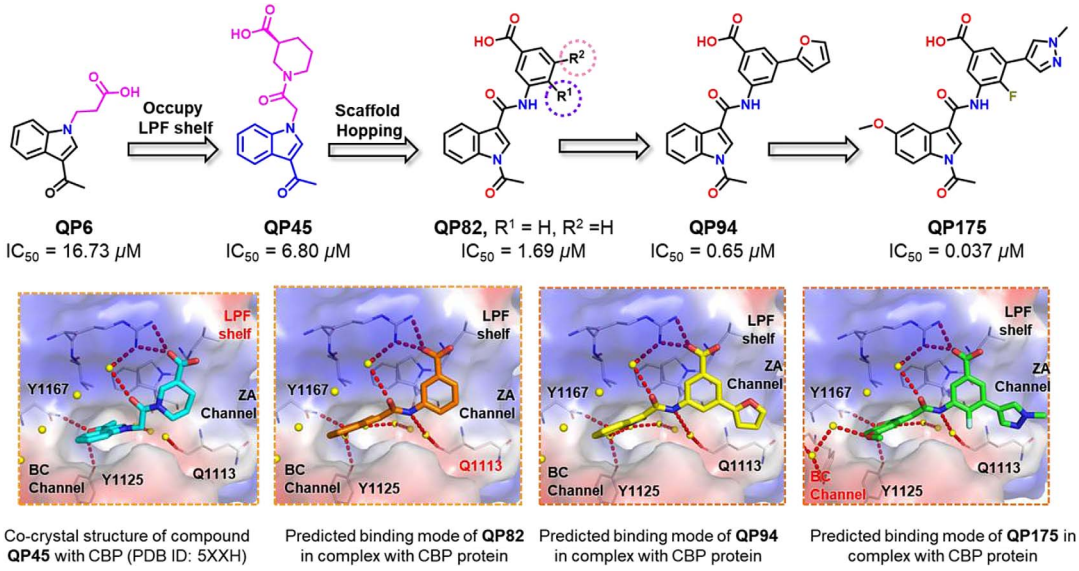


Figure 5. Flowchart summarizing the design of novel 1-acetylindolederivatives.

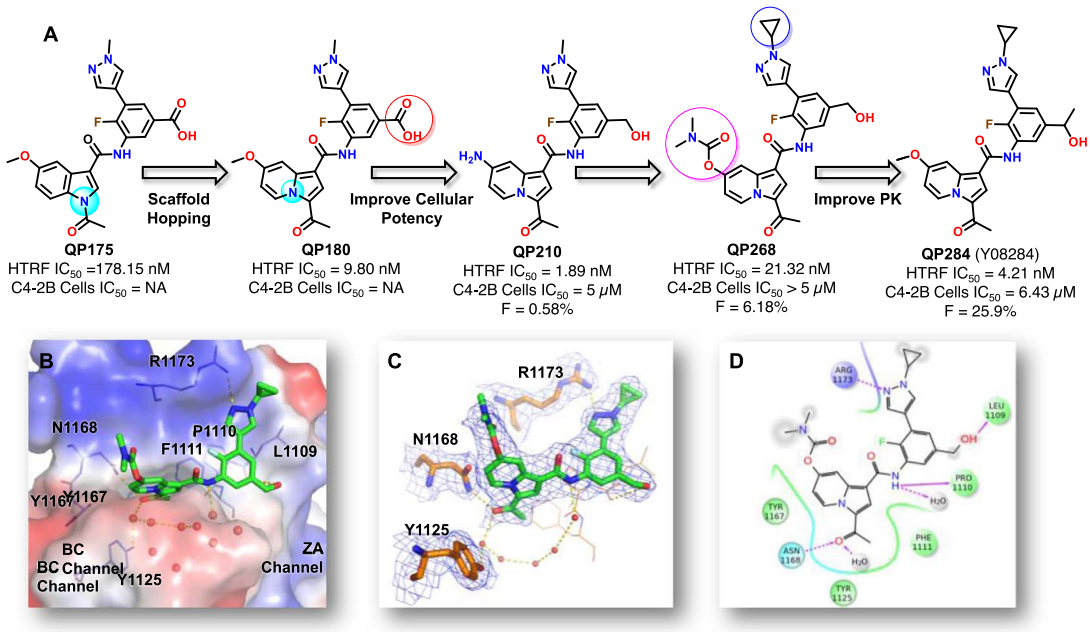


Figure 6. Design and structural optimization strategies of 1-(indolizin-3-yl)ethan-1-ones. (A) Design strategy of coupling 3-acetylindolizine derivatives. (B-D) Crystal structure of **QP268** bound to CBP bromodomain (PDB ID: 7EVJ).

the pharmacokinetic profiles without obviously affecting CBP bromodomain inhibitory potency. Therefore, compound **QP284** (Y08284) harboring a methyl group to $-CH_2OH$ group was designed and synthesized. **QP284** displayed strong CBP bromodomain binding affinity with an IC_{50} value of 0.0042 μM (HTRF) and good cellular activity with an IC_{50} value of 6.43 μM in C4-2B cells. Additionally, molecule **QP284** indicated favorable liver microsome stability, good cell permeability, and acceptable oral bioavailability (F = 25.9%). Moreover, an examination of a panel of 16 bromodomain-containing proteins indicated that compound **QP284** displayed good target selectivity for CBP over other bromodomains.

Based on the strong potency, reasonable target selectivity, and good drug-like properties, **QP284** was further used to explore the role of CBP bromodomain in the biology of prostate cancer [54]. The results indicated that **QP284** significantly inhibited the proliferation of AR-expressing prostate cancer cell lines (C4-2B, LNCaP, and 22Rv1). Compound **QP284** can inhibit colony formation and migration of prostate cancer cells. Also, compound **QP284** could repress AR target gene expression, as well as c-Myc expression in prostate cancer cell lines. Furthermore, **QP284** showed significant antitumor activity in a prostate cancer xenograft model. These findings indicated that CBP bromodomain is a potential target for prostate cancer treatment.

Perspective and summary

To date, much evidence has shown that CBP bromodomain plays a key role in the occurrence and development of a variety of diseases, including prostate cancer, leukemia, and breast cancer. Besides, clinical data have also indicated that the expression level of CBP bromodomain has a close relationship with the progression and prognosis of diseases [14]. Therefore, CBP is considered a potential and promising therapeutic target for human diseases. Over the past decades, researchers have made great efforts to develop novel CBP bromodomain inhibitors and explain the biological functions of CBP bromodomain. CBP bromodomain inhibitors have indicated potent inhibitory activity against some diseases. Until now, at least six representative scaffolds of CBP bromodomain inhibitors have been reported, some of which have weak affinities and nonspecific targeting. Therefore, there is an urgent need to develop more potent and selective CBP bromodomain inhibitors with novel scaffolds and drug-like properties to explore their therapeutic potential in different human diseases. Moreover, CBP-selective and p300-selective bromodomain inhibitors should be designed to study their therapeutic value in the same and/or different diseases.

Considering the current issues, many novel types of CBP inhibitors, such as PROTAC (proteolysis targeting chimeras) and allosteric inhibitors, are urgently needed. A PROTAC is a bifunctional small molecule composed of two ligands and a linker [62–64]. Rather than acting as a traditional molecule, a PROTAC works by inducing selective intracellular proteolysis. Currently, scientists have shown that degradation of target proteins could avoid drug resistance more effectively and has better anticancer effects than inhibition of target proteins. However, only one CBP bromodomain PROTAC molecule (dCBP-1) has been developed. Therefore, PROTACS deserves further investigation as a specific method for the development of novel CBP bromodomain inhibitors. Selective bromodomain inhibitors discovered all targeted the classic KAc recognition pocket, by which they could not distinguish with other bromodomains, increasing the possibility of off-target. Allosteric inhibitors could change the conformation of the bromodomain proteins to prevent the interactions between bromodomains and acetyllysine of histones through binding with the allosteric site. Allosteric inhibitors are common in kinases but rare in bromodomains. Recently, Liu et al. reported a BRD4(1)-selective inhibitor ZL0590 which is the first-in-class BRD4(1) inhibitor with a nonacetylated lysine binding site on BRD4(1) [65]. The result provided a structural basis for the discovery of allosteric inhibitors of CBP bromodomain.

In summary, considering the important role of CBP bromodomain in various diseases and the research status of its inhibitors, it is still necessary to develop more potent and more specific CBP bromodomain inhibitors, PROTACs, etc. In the review, we summarized the development of CBP bromodomain inhibitors in our group, including the SARs, binding modes, and pharmacological profiles. We believe that with further studies on the small molecule inhibitors, PROTACS, and crystal structures, more efficient and selective CBP inhibitors will be reported for the treatment of diseases with CBP as a potential therapeutic target.

Conflicts of interest

The authors declare that they do not have any conflict of interest.

Acknowledgements. This work was supported in part by grants from the National Natural Science Foundation of China (grant 22007088) the Guangdong Basic and Applied Basic Research Foundation (grant 2021A1515010085), the Science and Technology Program of Guangzhou (Grant 202102080016). The authors also gratefully acknowledge support from the Guangzhou Branch of the Supercomputing Center of Chinese Academy of Sciences.

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Cite this article as: Xiang Q, Zhou Y, Zhang Y & Xu Y. CBP/p300 bromodomain: new promising epigenetic target. Visualized Cancer Medicine. 2022. **3**, 3.