REVIEW
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Recent progress of small molecular HDAC modulators for cancer therapy and beyond

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Zhao CL and Chai QP wrote the manuscript and contributed to the manuscript equally; Zhang YJ contributed to reviewing and editing the paper. All authors read and approved the final manuscript.
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Abbreviations
AI, artificial intelligence; AML, acute myeloid leukemia; BRD4, bromodomain-containning protein 4; CRBN, cereblon; DMD, duchenne muscular dystrophy; CTCL, cutaneous T-cell lymphoma; DFMO, difluoromethyl-1,3,4-oxadiazole; DLBCL, diffuse large B cell lymphoma; HA, hydroximic acid; HAIRs,hydroxamic acids immobilized on resins; HAT, histone acetyltransferase; FEM1B, Fem-1 Homolog B; HDAC, histone deacetylase; IKZF, ikaros zinc finger; JAK, Janus kinase; LIFR, leukemia inhibitory factor receptor; PFBS, pentafluorobenzenesulfonamide; PROTAC, proteolysis targeting chimera; PK, pharmacokinetics; PTCL, peripheral T-cell lymphoma; MM, multiple myeloma; STAT, signal transducer and activator of transcription; SAR, structure-activity relationship; TNBC, triple negative breast cancer; VHL, Von Hippel–Lindau; ZBG, zinc-binding group.
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Abstract
The development of HDAC inhibitors holds great promise for cancer and other disease therapies. However, the approved HDAC inhibitors demonstrate low isoform selectivity, non-negligible off-target toxicity, unfavorable PK profiles, and poor efficacy against solid tumors. Additionally, the complicated HDAC biology involved in epigenetic functions and non-epigenetic cellular signaling pathways still remains poorly understood. These challenges indicate the urgent need for improved HDAC modulators, which can be not only potential therapeutics but also valuable chemical tools to further probe the biology of HDACs. In the review, we provided a summary of recently reported small molecular HDAC modulators, mainly including class-selective and isoform-selective HDAC inhibitors, slow-binding and covalent HDAC inhibitors, multitarget HDAC inhibitors, as well as HDAC PROTACs. The advantages and disadvantages of these small molecule HDAC modulators were also discussed. We hope this review will be informative for developing the next generation of small molecular HDAC modulators.

Keywords: Histone deacetylase (HDAC); small molecule modulator; multi-target inhibitor; proteolysis targeting chimera (PROTAC); cancer

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Introduction

Acetylation and deacetylation are two epigenetic modifications on histones, which are regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs can add acetyl groups to the lysine residues of histones, generally leading to the activation of gene expression, while HDACs are capable of removing the acetyl groups on histones, generally resulting in the repression of gene expression [1–4]. Besides their epigenetic roles, HDACs can also exert important effects on the post-translational modification of non-histone proteins. Consequently, HDACs play crucial roles in the regulation of both gene expression and protein functions [1, 4, 5].

Currently, 11 zinc-dependent human HDACs have been identified and grouped into three classes. Class I HDACs are composed of HDAC1, 2, 3, and 8, while class IV HDAC consists of sole isoform HDAC11. In addition, class II HDACs can be subdivided into class IIa (HDAC4, 5, 7, and 9) and class IIb (HDAC6 and 10) [1, 4, 5]. Due to their important functions in the regulation of both gene expression and protein functions, they have been considered promising therapeutic targets for many diseases mainly including various cancers, inflammatory diseases, neurodegenerative disorders, and viral infection. As a result, the development of biologically active compounds to target HDACs holds great promise for the treatment of these diseases. Most reported HDAC inhibitors fit well into a canonical pharmacophore model (using SAHA as a reference, Figure 1A), which includes a zinc-binding group (ZBG) enabling both chelation of the zinc ion and multiple hydrogen bond interactions with key residues in the active pocket, a cap structure responsible for the binding to the rim of HDAC on the other side as well as a suitable linker which can not only connect ZBG and the cap group but also occupy the hydrophobic tunnel (Figure 1B) [4, 6].

Up to now, six HDAC inhibitors have gained approval (Figure 1) [2, 4, 7]. In 2006, SAHA became the first FDA-approved HDAC inhibitor, which is used for the treatment of cutaneous T-cell lymphoma (CTCL). Later, romidepsin was approved by the FDA as a treatment for relapsed/refractory CTCL and relapsed/refractory peripheral T-cell lymphoma (PTCL) in 2009 and 2011, respectively. In 2014, belinostat and chidamide gained approval from the FDA and Chinese FDA for the treatment of relapsed or refractory PTCL, respectively, while panobinostat was approved to treat patients with multiple myeloma (MM) in 2015. In 2024, givinostat received its first approval from the FDA as a treatment for Duchenne muscular dystrophy (DMD). However, most of these approved HDAC inhibitors are often subjected to dose-limited toxicities, poor pharmacokinetic (PK) properties, and weak-to-modest patient benefits [4]. In addition, despite the promising efficacy against hematologic malignancies, these approved HDAC inhibitors have shown undesirable therapeutic efficacy against solid cancers [8, 9]. Inspiringly, combination treatment can significantly sensitize solid tumors to HDAC inhibitors via synergistic effects, thus providing a new avenue for solid tumor therapy. Notably, on the one hand, multi-target HDAC inhibitors can have comparable therapeutic efficacy in contrast to combination therapy. On the other hand, they may also circumvent unfavorable drug–drug interactions, and provide more predictable pharmacokinetics profiles as well as improved patient compliance [10, 11]. Therefore, the focus on the development of HDAC inhibitors has shifted towards targeting single HDAC isoenzymes, alternative ZBGs, slow-binding and covalent inhibition as well as multi-target HDAC inhibitors.

Notably, some HDAC isoenzymes can also mediate signals via non-enzymatic functions, which cannot be blocked by traditional active site-directed HDAC inhibitors [12–15]. Therefore, it is necessary to develop novel HDAC modulators, which can intervene in the deacetylase-independent functions of HDACs. The development of proteolysis targeting chimeras (PROTACs) represents a new paradigm in drug discovery. One PROTAC molecule comprises a target protein binder, an E3 ligase recruiter, and a linker [16, 17]. By hijacking the ubiquitin-proteasome system (UPS), PROTACs trigger the degradation of target proteins, thus being able to inhibit the scaffolding functions of target proteins [16, 17]. Interestingly, PROTACs hold promise of showing higher selectivity for homologous proteins than their corresponding protein binders [18, 19]. Therefore, the development of PROTAC-based HDAC modulators has also become a promising strategy for exploring the druggability of the deacetylase-independent functions of HDACs.

In this review, we summarized the recently reported small molecular HDAC modulators, mainly including class-selective and isoform-selective HDAC inhibitors, slow-binding and covalent HDAC inhibitors, multitarget HDAC inhibitors, as well as HDAC PROTACs. Future perspectives of small molecule HDAC modulator design will also be discussed.

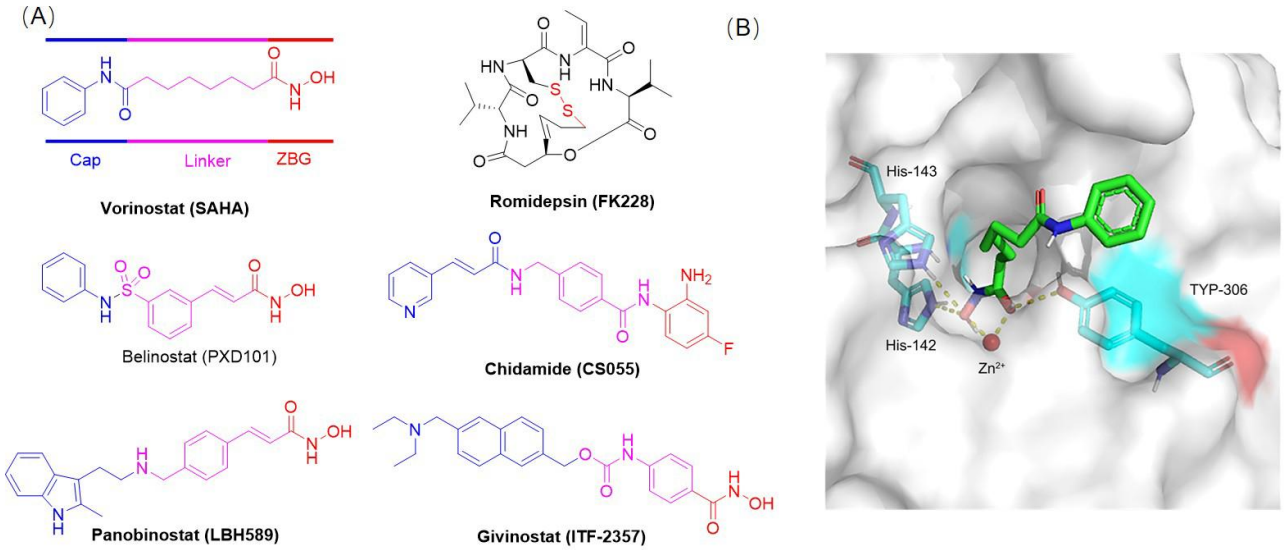

Figure 1 (A) The canonical pharmacophoric model of HDAC inhibitors and chemical structures of approved HDAC inhibitors. ZBG is marked in red, the linker is marked in pink, and the cap group is marked in blue. (B) The crystal complex of SAHA with HDAC8 (PDB ID: 1T69) [20]. SAHA was shown as green sticks. The coordination of zinc ion and hydrogen bond interactions were shown as yellow dashed lines. Zinc ion was shown as red spheres.

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Class-selective and isoform-selective HDAC inhibitors

Although five HDAC inhibitors have gained approval for various cancer therapies, they are normally considered as non-selective HDAC inhibitors, which have numerous serious side effects, probably due to their pan-HDAC inhibition [21]. Many efforts have been made to afford class-selective and isoform-selective HDAC inhibitors via the use of alternative ZBGs as well as structural modifications of the linker and cap group [22]. Moreover, structural analysis of available HDAC crystal structures, mainly including both conserved and isoform-specific structural and mechanistic features, also helps rationalize selective HDAC inhibitors [23]. Based on these strategies, some class-selective and isoform-selective HDAC inhibitors, such as class I HDAC inhibitor **1** [24], class IIa HDAC inhibitor **2** [25], class IIb HDAC inhibitor **3** [26], selective HDAC3 inhibitor **4** [27], selective HDAC6 inhibitor **5** [28], selective HDAC8 inhibitor **6** [29], selective HDAC10 inhibitor **7** [30] as well as selective HDAC11 inhibitor **8** [31], have been developed (Figure 2). Recent progress of isoform-selective HDAC inhibitors has been well reviewed [22, 32–38].

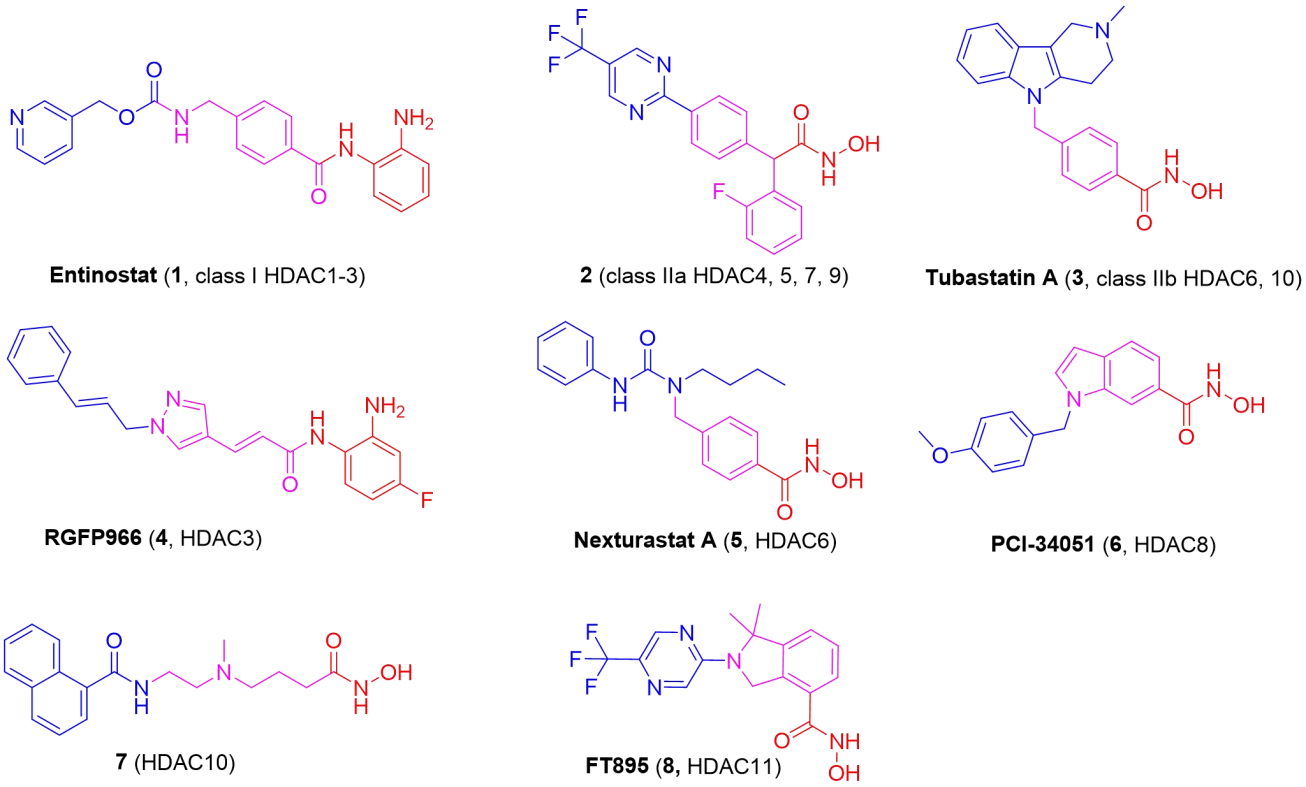


Figure 2 The chemical structures of representative class-selective and isoform-selective HDAC inhibitors. These HDAC inhibitors have excellent class-selectivity or isoform-selectivity and nanomolar-level inhibitory potency. ZBG is marked in red, the linker is marked in pink, and the cap group is marked in blue.

Slow-binding and covalent HDAC inhibitors

Slowing-binding HDAC inhibitors

Although hydroxamic acid is widely used as ZBG in HDAC inhibitor design, hydroxamate-based HDAC inhibitors have been connected with concerns about their clinical application. For instance, the hydroxamic acid group is liable to multiple metabolic processes, thus resulting in poor pharmacokinetics (PK) [39]. In addition, the mutagenicity and genotoxicity effects of the hydroxamic acid group also hinder the clinical use of hydroxamate-based HDAC inhibitors [40]. It should be mentioned that the clinical side effects associated with hydroxamate-based HDAC inhibitors may also originate from off-target effects [41–45]. Therefore, there is a need to explore alternative ZBGs to provide safer HDAC inhibitors with favorable PK properties and improved affinities for Zn^{2+}. In the past decades, besides benzamide, several novel ZBGs have been reported and reviewed, mainly including trifluoromethyl ketone, alkyl hydrazides, and fluorinated oxadiazoles [46–48]. Notably, some non-hydroxamate ZBGs endow HDAC inhibitors with slow-binding and dissociating properties. Compared with hydroxamate-based fast-binding HDAC inhibitors, slow-binding inhibitors do not reach equilibrium instantly, which enables gradually increased potency during incubation. Owing to this unique characteristic, the target residence time of slow-binding HDAC inhibitors varies depending on different HDACs, which may help to improve class/isoform selectivity [49]. In addition, slow-binding HDAC inhibitors may also hold the advantages of more durable pharmacological effects, lower effective doses as well as fewer adverse effects [49, 50]. Notably, the above similar advantages could also be observed in covalent inhibitors because they might lead to irreversible target binding and consequent longer target residence time. The chemical structures of representative slow-binding HDAC inhibitors (compounds **9**–**22**) and covalent HDAC inhibitors (**23**–**27**) are illustrated in Figure 3 and Figure 4, respectively.

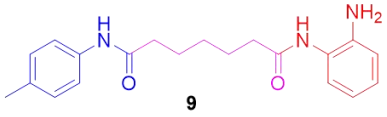
Benzamide-based inhibitors were initially considered weak HDAC inhibitors with high micromolar potency. However, due to the discrepancy between in vitro/in vivo efficacies and HDAC inhibition, this raised the authors' interest in investigating the inhibitory properties of HDAC inhibitor **9** [51]. Unlike SAHA, compound **9** exhibits time-dependent inhibition, significantly improving potency with preincubation. For example, HDAC1 IC_{50} is improved from 460 nM (without preincubation) to 138 nM (after 15 min), while HDAC3 inhibition remains incomplete even after hours, highlighting its potential as a slow-binding inhibitor. In addition, **9** inhibited HDAC3

with an IC_{50} value of 380 nM after 3 h preincubation, which is a 15-fold decrease in contrast to the IC_{50} measured without preincubation [51]. These results indicate that a simple investigation of IC_{50} determinations might be an unreliable method to characterize HDAC inhibitors. Instead, *Ki* and the on-rates and off-rates should be used in inhibitor evaluation, which are intrinsic properties of the particular protein-inhibitor pair [51]. Followed by the characterization of benzamides, some other chemotypes have also been identified as slow-binding HDAC inhibitors. Liu et al. reported a series of 2-substituted benzamide derivatives as ZBGs, which afforded potent class I HDAC inhibitors [52]. The 2-methylthiobenzamide **10** showed potent HDAC3 inhibition with > 300-fold selectivity over other HDAC isoenzymes. Interestingly, the replacement of the 2-methylthio of **10** with a 2-hydroxy benzamide led to **11**, which retained HDAC3 potency but lost selectivity over HDAC 1 and 2. [52]. Olsen group performed a detailed kinetic evaluation of the trifluoromethyl ketone version of SAHA HDAC inhibitor **12** [53]. Unlike SAHA, compound **12** showed a fast-on/fast-off mechanism against HDAC4 and HDAC7, whereas provided slow-binding mechanisms for both class-I and class-IIb enzymes [53]. Another chemotype of slow-binding HDAC inhibitors is alkyl hydrazide. In 2015, through high-throughput screening, the hydrazide UF010 (**13**) as a selective class I HDAC inhibitor was identified by Liao and his colleagues [54]. UF010 inhibited HDAC1 and HDAC2 with comparable potency but exhibited selectivity for HDAC3. However, the n-propyl analog of UF010 **SR-3212** retained HDAC3 inhibition but demonstrated higher selectivity over HDAC1 and HDAC2. Interestingly, the authors proposed that these hydrazides are competitive inhibitors with a fast-on/slow-off HDAC-binding mechanism [54]. However, Li et al. reported another hydrazide-based HDAC inhibitor **15** whose antitumor mechanism varies depending on p53 status in leukemia and prostate cancer cells [55]. Notably, compound **15** provided enzyme-inhibitor preincubation time-dependent IC_{50} values, suggesting that **15** is a slow, tight-binding inhibitor of class I HDACs [55]. Such binding mechanism has also been observed in the case of recently reported hydrazide-based class I HDAC inhibitor **16** [56]. Notably, compound **16** could inhibit HDAC1–3, especially HDAC3 in a time-dependent manner and showed strong synergism with cisplatin in cisplatin-resistant cancer cells [56]. In addition to hydrazide-based HDAC1–3 inhibitors, some hydrazide-based isoform-selective HDAC inhibitors have been developed. For instance, compound **17** incorporating a large spatial cap group and short ethyl hydrazide was identified as the first selective HDAC6 inhibitor (IC_{50} = 0.019 μM) [57]. Notably, both the PK properties and oral bioavailability of hydrazide-based **17** outperformed the hydroximic acid-based counterparts [57]. In addition, Sun et al. reported a novel series of hydrazide-based class I HDAC inhibitors with the *n*-hexyl side chain attached to the hydrazide moiety, affording a selective HDAC8 inhibitor **18**, which has T cell modulatory effects [58]. In 2019, Son et al. reported the development of HDAC11-specific inhibitor SIS17 (**19**), which showed comparable HDAC11 inhibitory activity (IC_{50} = 0.83 μM) with the well-known selective HDAC11 inhibitor FT895 (IC_{50} = 0.74 μM) using myristoyl-H3K9 as the substrate. It is worth noting that short ethyl hydrazides inhibit HDAC6, while *n*-propyl hydrazides inhibit HDAC1–3, *n*-hexyl hydrazides inhibit HDAC8, and long-chain *N*-alkyl hydrazides, such as SIS17, preferentially inhibit HDAC11. The hydrazides as HDAC inhibitors have been recently reviewed [59].

Besides hydrazides, substituted oxadiazoles have also drawn attention as a promising novel HDAC inhibitor chemotype. In 2022, Cellupica et al. identified a difluoromethyl-1,3,4-oxadiazole (DFMO) based HDAC6 inhibitor **20**, a potent inhibitor with over 100-fold selectivity for HDAC6 over all other HDACs [60]. Further experiments demonstrate that **20** is a slow-binding substrate analog of HDAC6 that undergoes an HDAC6-catalyzed ring open reaction [60]. Shortly later, a novel DMFO-based selective HDAC6 inhibitor **21** was reported by Ripa et al [61]. Similar to **20**, **21** cannot inhibit HDAC6 until they form a tight and long-lived enzyme–inhibitor complex through chemical reactions catalyzed by HDAC6 [61]. Such a mechanism of action was also observed in another novel DFMO-based selective HDAC6 inhibitor **22,** which was reported by the Hansen group at the same time [62]. Compared to hydroxamate-based HDAC6 inhibitors, DFMO-based HDAC6 inhibitors hold some advantages mainly including higher oral bioavailability and lower in vivo clearance. However, it should be mentioned that the oxadiazoles are susceptible to degradation in water solution and the generation of potentially toxic degradation products, hindering the developability for chronic diseases [61].

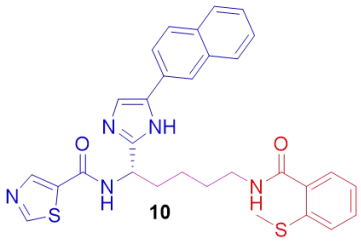
Covalent HDAC inhibitors

In addition to slow-binding reversible HDAC inhibitors, research is also focusing on the development of irreversible covalent strategies, which may enable full occupancy and complete inactivation of the targets as well as prolonged duration of action [50]. In 2015, our research group reported a novel phenylsulfonylfuroxan-based nitric oxide (NO) donor- HDAC inhibitor hybrid **23** [63]. Interestingly, **23** exhibited potent antiproliferative activities, which can be diminished by the NO scavenger hemoglobin [63]. Interestingly, further experiments have demonstrated that **23** is an irreversible HDAC6 and class I HDACs inhibitor, probably owing to the S-nitrosylation of HDACs [64]. In our more recent effort, a new HDAC inhibitor-NO donor hybrid **24** was developed via structural modification of compound **23**, which exhibited excellent HDAC6 inhibitory activity and selectivity [64]. Considering that there are several conserved Cys residues surrounding the binding site of HDAC1, HDAC2, and HDAC3, Raouf et al. designed and characterized the first class I HDACs selective covalent HDAC inhibitors via incorporation of a Cys-reactive motif to the cap group of the modified HDAC1–3 inhibitor entinostat [65]. The lead compound YSR734 (**25**) possesses an SNAr-reactive pentafluorobenzenesulfonamide (PFBS) electrophile, which enables covalently inhibiting HDAC1–3 and showing longer-lasting effects in cells [65]. In 2016, the Meyer group found that the benzothiazine-imine **26** is a potent and selective HDAC8 inhibitor with an unprecedented chemical scaffold lacking a classical ZBG [66]. This interesting finding raised the authors' interest in investigating the HDAC8 inhibition mechanism. The authors found that **26** is an irreversible inhibitor of HDAC8, which can be reversed by reducing agents and involves Cys153 in the active site and the adjacent Cys102 [67]. In a more recent effort, 3-ethynylmethylpyridinium **27** was developed as a covalent HDAC8 inhibitor via covalent binding Cys153 by Keeley et al [68]. These efforts provide a strategy to selectively target HDACs by use of enzyme-specific residues.



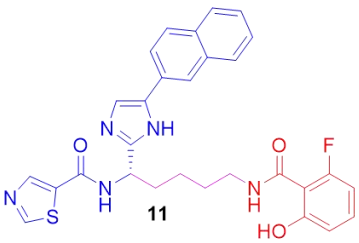
9

HDAC1 IC_{50} = 138 nM
HDAC3 IC_{50} = 380 nM



10

HDAC1: IC_{50} = 20 μM
HDAC3: IC_{50} = 29 nM
HDAC2/6/8: IC_{50} > 20 μM

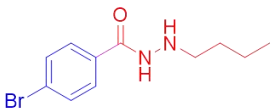


11

HDAC1: IC_{50} = 9.7 nM
HDAC2: IC_{50} = 29 nM
HDAC3: IC50 = 7.6 nM
HDAC6: IC_{50} = 9 μM
HDAC8: IC_{50} > 45 μM

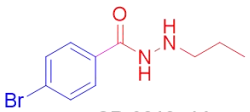
12

HDAC1: Ki = 9.8 μM
HDAC2: Ki = 11 μM
HDAC3: Ki ~ 11 nM
HDAC4: Ki = 5.1 nM
HDAC6: Ki = 4.5 μM
HDAC7: Ki = 4.7 nM
HDAC8: Ki ~ 33 nM



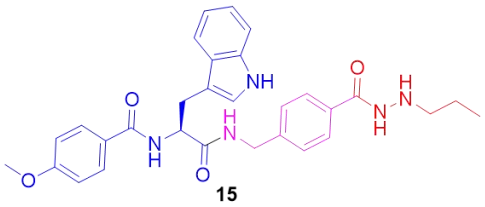
UF010 (13)

HDAC1: IC_{50} = 0.46 μM
HDAC2: IC_{50} = 1.3 μM
HDAC3: IC_{50} = 0.19 μM
HDAC6: IC_{50} = 9.1 μM
HDAC8: IC_{50} = 2.8 μM



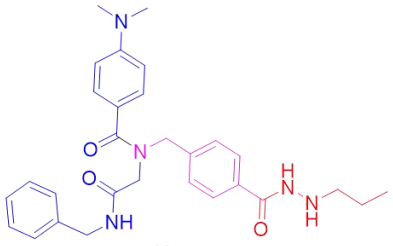
SR-3212 (14)

HDAC1: IC_{50} = 1.7 μM
HDAC2: IC_{50} = 3.9 μM
HDAC3: IC_{50} = 0.22 μM
HDAC6: IC_{50} = 4.6 μM



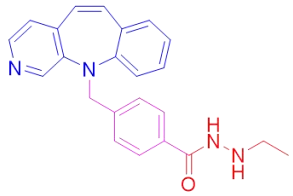
15

HDAC1: IC_{50} = 9.5 nM
HDAC2: IC_{50} = 28 nM
HDAC3: IC_{50} = 1.4 nM
HDAC4/5/6/7/9: IC_{50} > 50 μM
HDAC8: IC_{50} = 0.56 μM



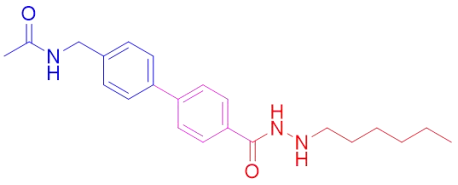
16

HDAC1: IC_{50} = 27 nM
HDAC2: IC_{50} = 141 nM
HDAC3: IC_{50} = 4 nM
HDAC4/6/8: IC_{50} > 10 μM



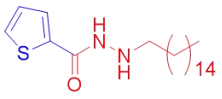
17

HDAC1: IC_{50} = 1.5 μM
HDAC2: IC_{50} = 2.1 μM
HDAC3: IC_{50} = 1.0 μM
HDAC6: IC_{50} = 0.019 μM
HDAC4/5/7/8/9/11: IC_{50} > 5 μM



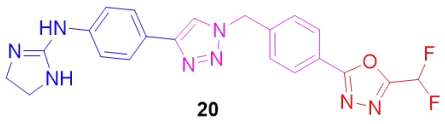
18

HDAC1: IC_{50} = 1.8 μM
HDAC2: IC_{50} = 12 μM
HDAC8: IC_{50} = 0.036 μM
HDAC11: IC_{50} = 0.18 μM
HDAC3/4/6: IC_{50} > 20 μM



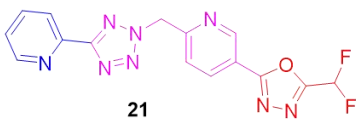
19

HDAC11: IC_{50} = 0.83 μM



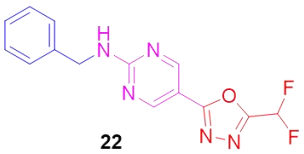
20

HDAC1-5: IC_{50} > 100 μM
HDAC6: IC_{50} = 7.7 nM
HDAC8-11: IC_{50} > 100 μM



21

HDAC1-5: IC_{50} > 100 μM
HDAC6: IC_{50} = 190 nM
HDAC8-11: IC_{50} > 100 μM



22

HDAC1-4: < 15% inhibition @ 10 μM
HDAC6: IC_{50} = 193 nM

Figure 3 The chemical structures of representative slow-binding HDAC inhibitors. These HDAC inhibitors may have improved class/isoform selectivity, more durable pharmacological effects, lower effective doses as well as fewer adverse effects. ZBG is marked in red, the linker is marked in pink, and the cap group is marked in blue. The HDAC inhibitory activities are evaluated by the determination of IC_{50} values.

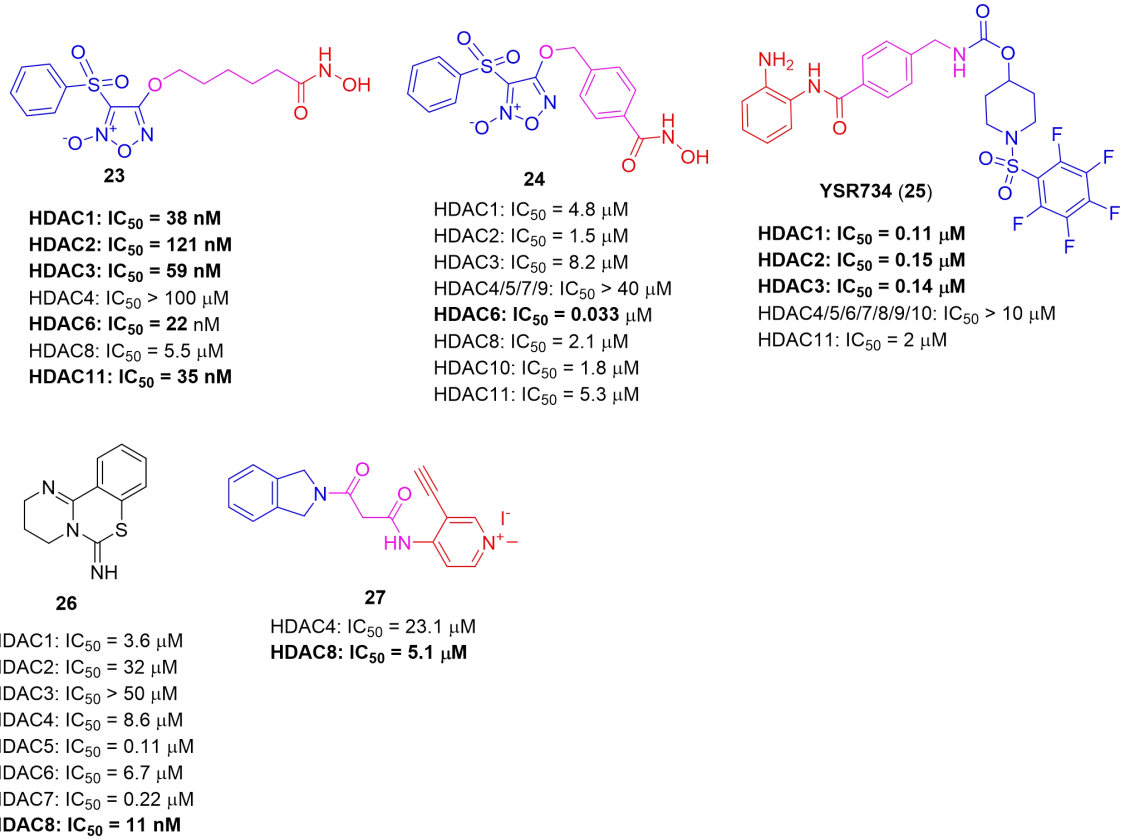


Figure 4 The chemical structures of representative covalent HDAC inhibitors. These HDAC inhibitors highlight the potential of selectively targeting HDACs by use of enzyme-specific residues. ZBG is marked in red, the linker is marked in pink, and the cap group is marked in blue. The HDAC inhibitory activities are evaluated by the determination of IC_{50} values.

Multi-target HDAC inhibitors

Despite the promising efficacy against hematologic malignancies, these approved HDAC inhibitors have shown undesirable therapeutic efficacy due to multiple resistance mechanisms. One of these mechanisms is BRD4-LIFR-JAK1-STAT3 signaling pathway in which HDAC inhibition increases histone acetylation at the LIFR gene promoter, which recruits bromodomain protein BRD4 and upregulates LIFR expression, followed by the activation of JAK1-STAT3 signaling pathway and the promotion of antiapoptotic genes expression, thus leading to the poor therapeutic efficacy of HDAC inhibitors in solid tumors [69]. Importantly, JAK1 or BRD4 inhibition sensitizes breast cancer to HDAC inhibitors, highlighting the therapeutic potential of concurrent inhibition of HDAC with JAK1 and/or BRD4 for the treatment of solid tumors [69]. Due to the advantages of multi-target strategy compared to drug combination, research and development of multi-target HDAC inhibitors blocking BRD4-LIFR-JAK1-STAT3 signaling pathway has become a promising strategy to sensitize solid tumors to HDAC inhibitors. The representative multi-target HDAC inhibitors are illustrated in Figure 5. These multi-target HDAC inhibitors also fit well into the canonical pharmacophore model as shown in Figure 1A.

HDAC/JAK dual inhibitors

In 2019, our group reported a series of JAK and HDAC dual inhibitors [70]. The representative compound **28** possessed potent proapoptotic activity, but a moderate in vivo antitumor potency against hematological malignancies [70]. Nevertheless, the antitumor activity against triple-negative breast cancer (TNBC) cell line MDA-MB-231 of compound **28** was unsatisfactory, probably due to the incomplete blockade of the drug-resistant pathway induced by HDAC inhibition [70]. Then, another JAK/HDAC dual inhibitor **29** was developed, which displayed potent antiproliferative and proapoptotic activities in triple-negative breast cancer cell lines [71]. Similar to **28**, **29** did not show significantly improved antitumor activity against multiple TNBC cell lines in contrast to SAHA [71]. Fedratinib is an approved JAK inhibitor, but it can also inhibit BRD4 at therapeutic concentrations [72]. In 2023, our group reported a novel series of Fedratinib derivatives with HDAC/JAK/BRD4 triple inhibitory activity, which are expected to have higher antitumor potency compared to HDAC/JAK inhibitors [73]. The representative compound **30** could simultaneously inhibit HDACs and the BRD4-LIFR-JAK1-STAT3 signaling pathway, which exhibited over 10-fold more potent than SAHA. Notably, compound **30** has acceptable toxicity and promising both in vitro and in vivo antitumor potency, which warrants further research and development. In the same year, another series of Fedratinib-based HDAC/JAK dual inhibitors were developed by Qiu et al [74]. Among them, **31** and **32** showed both potent HDAC and JAK inhibition and exhibited remarkable antiproliferative activity in both blood tumors and solid tumors [74].

HDAC/BRD4 dual inhibitors

Besides HDAC/JAK dual inhibitors, several HDAC/BRD4 dual inhibitors have also been reported. In 2020, He et al. reported a series of novel HDAC/BRD4 dual inhibitors for the treatment of pancreatic cancer [75]. The lead compound **33** had excellent and balanced HDAC1 and BRD4 inhibition and demonstrated excellent antitumor potency [75]. Another series of HDAC/BRD4 dual inhibitors were developed by Pan et al [76]. The representative compound **34** showed potent antitumor activities against colorectal carcinoma via inducing autophagic cell death in both in vitro and in vivo models [76]. In the same year, Chen et al. identified another HDAC/BRD4 dual inhibitor **35**, which exhibited synergistic effects against MV4–11 cells [77].

HDAC/STAT3 dual inhibitors

The natural product flavones could block STAT3-mediated oncogenic signaling pathways via various mechanisms. On the basis of the structure of flavones, Wei et al. developed a series of HDAC/STAT3 dual inhibitors [78]. In particular, compound **36** could potently inhibit the activity of HDAC1–3 and HDAC6 and demonstrated excellent antiproliferative activities against various solid tumor cells [78]. In 2021, Ren et al. developed a novel series of HDAC/STAT3 dual inhibitors by merging the pharmacophore of the HDAC inhibitor SAHA into the STAT3 inhibitor pterostilbene [79]. The representative compound **37** could not only show potent both HDAC and STAT3 inhibition but also potent anti-proliferative effects in both in vivo and in vitro [79]. In a more recent effort, Mo et al. reported a novel series of HDAC/STAT3 dual inhibitors based on a natural product isoalantolactone (IAL), which was recently identified as a STAT3 inhibitor. One excellent compound **38** demonstrated potent HDAC and STAT3 inhibition and exhibited stronger antitumor potency than IAL and SAHA via autophagy and apoptosis. Besides these abovementioned multi-target HDAC inhibitors, there are many other multi-target HDAC inhibitors, which have been described in detail [80–84].

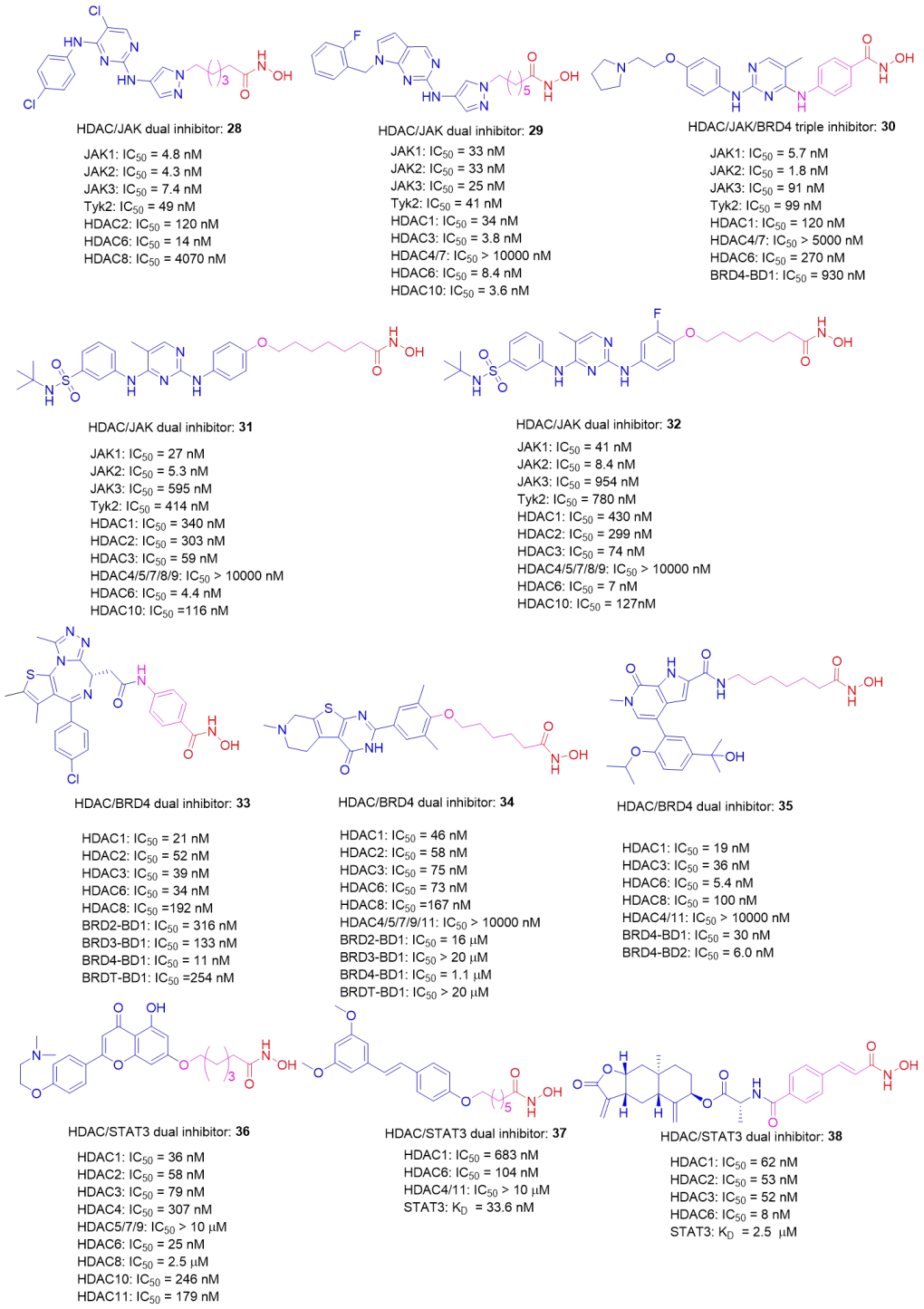


Figure 5 The chemical structures of representative multi-target HDAC inhibitors. These hybrid HDAC inhibitors showed potent antiproliferative activities against various cancers via blocking BRD4-LIFR-JAK1-STAT3 signaling pathway. ZBG is marked in red, linker is marked in pink, and cap group is marked in blue. The corresponding target inhibitory activities are evaluated by the determination of IC_{50} or K_D values.

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HDAC PROTAC

Some HDAC isoenzymes can also mediate signals via non-enzymatic functions, which cannot be blocked by traditional active site-directed HDAC inhibitors. This indicates the need for novel drug modulators to explore the druggability of the deacetylase-independent functions of HDACs. PROTAC represents a novel drug modality in drug discovery. By hijacking the ubiquitin-proteasome system (UPS), PROTACs trigger the degradation of target proteins, thus being able to inhibit scaffolding functions of target proteins. Interestingly, PROTACs can also show higher selectivity for homologous proteins than their corresponding protein binders. To date, many HDAC PROTACs have been reported [85–87], mainly including PROTACs-targeting class I HDACs, PROTACs-targeting class IIa HDACs, and PROTACs-targeting class IIb HDACs.

PROTACs-targeting class I HDACs

Class I HDACs consist of HDAC1, HDAC2, HDAC3, and HDAC8, which play important roles in various diseases. Although HDAC1 and HDAC2 efficiently hydrolyze acetyl lysine peptide substrates on their own in vitro, they predominantly exist in the nucleus as homo- and heterodimer constituents of the NuRD, Sin3A, CoREST, MiDAC, and MIER transcriptional repressor complexes [1]. Like HDAC1/HDAC2, HDAC3 is ubiquitously expressed and involved in the deacetylation of histones and some other nuclear non-histone substrates including STAT3 and FOXP3 [1]. HDAC8 is a unique class I HDAC and is located in both the nucleus and the cytoplasm. Currently, it remains unclear whether histones are bona fide HDAC8 substrates [37, 88]. Interestingly, the fatty acid deacylation mediated by HDAC8 is also physiologically relevant [89].

Recently, some class I HDAC-targeting PROTACs have been reported. The chemical structures and relevant degradation potency are described in Table 1. In 2020, Sinatra et al. used hydroxamic acids immobilized on resins (HAIRs) approach to get an efficient HDAC PROTAC **39**, which could dose-dependently trigger HDAC1 and HDAC6 degradation in the AML cell line HL60 [90]. Instead of using a hydroximic acid-based HDAC binder, Smalley et al. reported a series of PROTACs of class I HDAC 1, 2, and 3 [91]. The most potent PROTAC **40** consists of a benzamide-based HDAC binder, an alkyl linker, and the von Hippel-Lindau (VHL) E3 ligand. Nearly complete degradation of both HDAC1 and HDAC2 was observed after treatment of 10 μM of **40** in HCT116 cells, while HDAC3 levels were also decreased, to a lesser extent [91]. Similarly, Sinatra et al. developed another series of HDAC PROTACs [92]. PROTAC **41** could induce degradation of HDAC1 and HDAC 3 at low micromolar concentrations. Interestingly, changing the linker attachment position of the VHL ligand led to PROTAC **42**, which could selectively reduce HDAC3 levels in HCT116 cells [92]. More recently, Feller et al. developed the first Fem-1 homolog B (FEM1B)-recruiting HDAC degraders [93]. The representative PROTAC **43** showed substantial HDAC1 degradation, while HDAC2 and HDAC3 were also degraded upon treatment of **43** in MM.1S cells. Unlike the previously reported HDAC6 degrader **64** (Table 3) using the same HDAC binder [94], the FEM1B-based PROTAC **43** showed selective HDAC1–3 degradation [93]. In 2020, the Dekker group reported a benzamide-based HDAC PROTAC **44**, which selectively triggers HDAC3 degradation in RAW 264.7 macrophages [95]. By replacing the CRBN ligand with the VHL ligand, the Dekker group reported another series of HDAC3 PROTACs [96]. The hydrazide-based PROTAC **45** could achieve nearly complete HDAC3 degradation in both THP-1 cells and human primary macrophages. Interestingly, **45** showed potent antiinflammatory activities in both THP-1-derived M1-like macrophages and M1-like macrophages derived from human primary macrophages [96]. However, HDAC8 degradation was also observed upon treatment of **45** at high concentrations. Another selective HDAC3 PROTAC **46** was reported by Xiao et al [97]. PROTAC **46** induced HDAC3 degradation with a DC_{50} of 42 nM in MDA-MB-468 cells and more potently inhibited cancer cell proliferation than its proteolysis-inactive counterpart. Later, Xiao et al. discovered a potent and selective dual HDAC3 and HDAC8 degrader **47** [98]. However, their degradation induced by **47** neither led to histone hyperacetylation nor significantly perturbed the transcriptome. Besides PROTACs-targeting HDAC1–3, there are also several HDAC8 PROTACs. The first reported HDAC8 PROTAC **48** was developed by Chotitumnavee et al [99]. PROTAC **48** induced HDAC8 degradation with a high nanomolar range DC_{50} value and inhibited the growth of T-cell leukemia Jurkat cells [99]. Sun et al. reported a novel series of CRBN-recruiting HDAC8 PROTACs [100]. Among them, PROTAC **49** was identified as the most potent HDAC8 degrader (DC_{50} = 147 nM, D_{max} = 93%) without significant effect on HDAC1 and HDAC3 in HCT116 cells [100]. However, HDAC8 levels recovered after 24 h treatment of **49**. In addition, the antiproliferative activities of **49** against HCT116 cells have not been investigated. Sippl's group reported another HDAC8 PROTAC **50** to explore its anti-neuroblastoma activity [101]. Zhu's group reported a new HDAC8 PROTAC **51**, which induced HDAC8 degradation in A549 cells but showed limited HDAC8 degradation in Jurkat cells [102]. In 2023, the Dekker group reported another HDAC8 **52** with DC_{50} values of low nanomolar range in both MDA-MB-231 cells and Jurkat cells [103]. However, HDAC6 degradation was also observed upon **52** treatments, but to a lesser extent. However, PROTAC **52** showed poor antiproliferative activities against MDA-MB-231 cells, while about 10-fold more potent antiproliferative activities against Jurkat cells than the inhibitor [103]. In a more recent effort, they developed a series of hydrazide-based HDAC8 PROTACs [104]. The most potent HDAC8 degrader **53** provided low nanomolar level DC_{50} values in various cell lines [104]. It is worth noting that **53** is capable of increasing the intracellular levels of both Ac-SMC3 and Ac-Histone, which is due to HDAC8 degradation and off-target HDAC inhibition, respectively [104]. However, the histone hyperacetylation induced by off-target HDAC inhibition of **53** contributed mainly to the observed antiproliferative activities [104]. Another hydrazide-based HDAC8 PROTAC **54** also showed similar results [105].

Table 1 Representative PROTACs targeting Class I HDACs with their degradation efficiencies and selectivity profiles

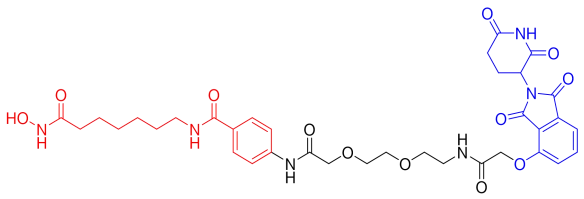
ID	Structures	Targets (Activities)	Ref.
39		HDAC1 and HDAC6	[90]

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Table 1 Representative PROTACs targeting Class I HDACs with their degradation efficiencies and selectivity profiles (*continued*)

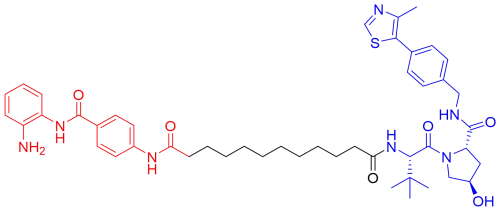
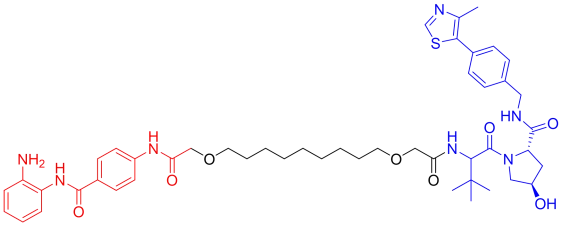
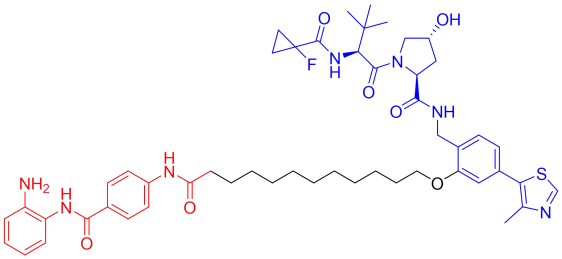
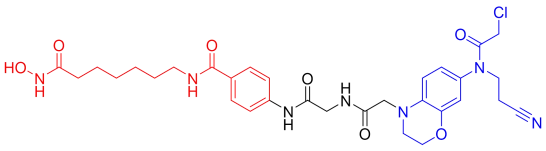
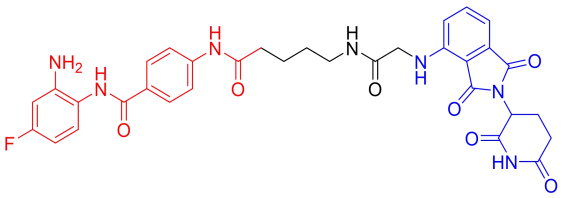
ID	Structures	Targets (Activities)	Ref.
40		HDAC1 and HDAC2	[91]
41		HDAC1 (DC_{50} = 0.91 μM, D_{max} = 74%) HDAC2 (DC_{50} = 4.20 μM, D_{max} = 56%) HDAC3 (DC_{50} = 0.64 μM, D_{max} = 59%)	[92]
42		HDAC3 (DC_{50} = 0.44 μM, D_{max} = 77%)	[92]
43		HDAC1 (DC_{50} = 257 nM, D_{max} = 85%) HDAC2 and HDAC3	[93]
44		HDAC3 (DC_{50} = 0.32 μM)	[95]

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Table 1 Representative PROTACs targeting Class I HDACs with their degradation efficiencies and selectivity profiles (*continued*)

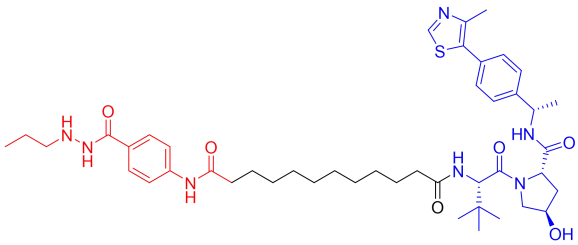
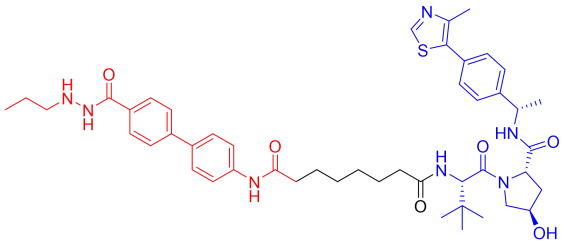
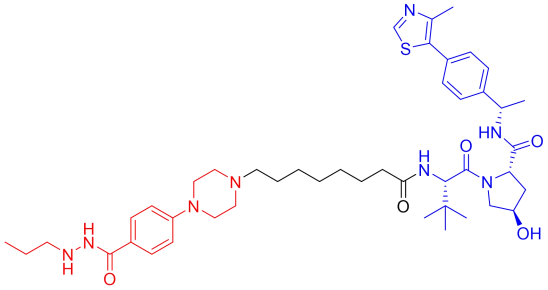
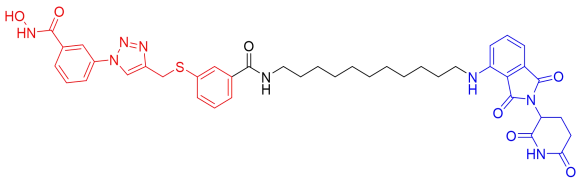
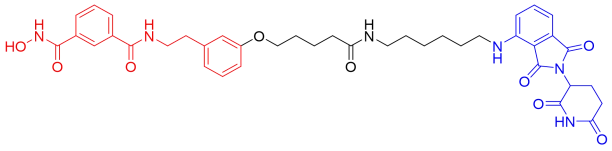
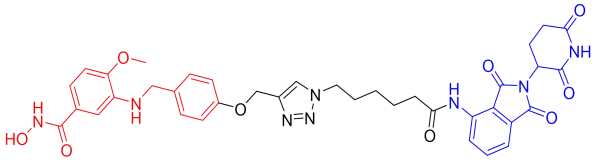
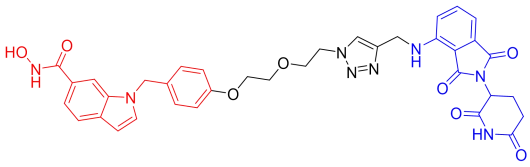
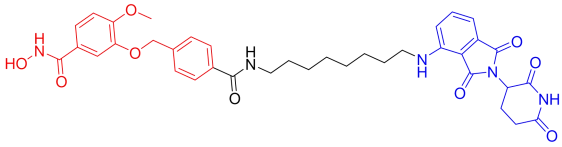
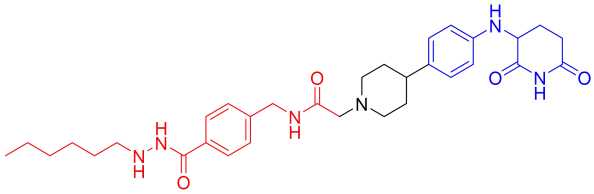
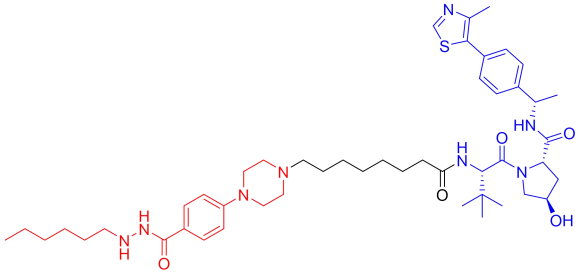
ID	Structures	Targets (Activities)	Ref.
45		HDAC3 (DC_{50} = 0.60 nM, D_{max} = 90%)	[96]
46		HDAC3 (DC_{50} = 42 nM)	[97]
47		HDAC3 (DC_{50} = 1.70 nM, D_{max} = 95%) HDAC8 (DC_{50} = 6.10 nM, D_{max} = 95%)	[98]
48		HDAC8 (DC_{50} = 702 nM)	[99]
49		HDAC8 (DC_{50} = 147 nM, D_{max} = 93%)	[100]

Table 1 Representative PROTACs targeting Class I HDACs with their degradation efficiencies and selectivity profiles (*continued*)

ID	Structures	Targets (Activities)	Ref.
50		HDAC8 (70% degradation at 10 μM)	[101]
51		HDAC8 (DC_{50} = 580 nM, D_{max} = 95%)	[102]
52		HDAC8 (DC_{50} = 4.70 nM, D_{max} = 95%) HDAC6 (DC_{50} = 78.5 nM, D_{max} = 76%)	[103]
53		HDAC8 (DC_{50} = 0.32 nM, D_{max} = 97%)	[104]
54		HDAC8 (DC_{50} = 2.6 nM, D_{max} = 95%)	[105]

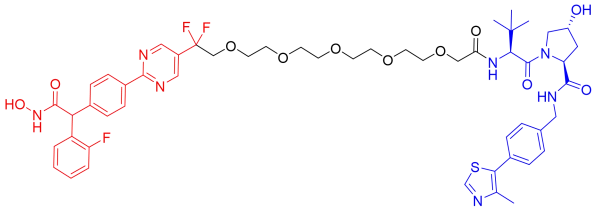
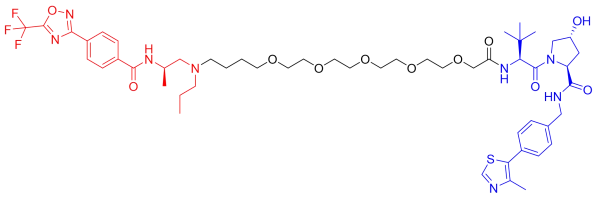
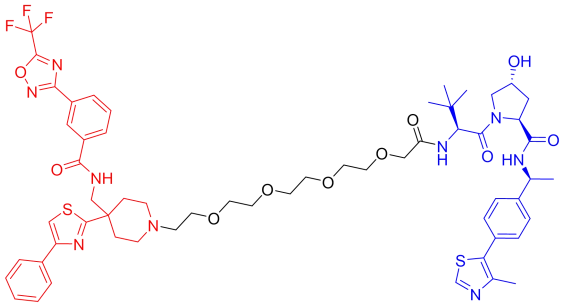
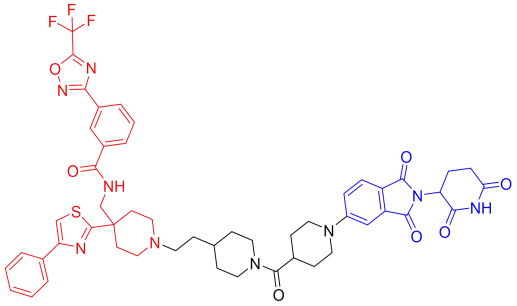
HDAC binder is marked in red, the linker is marked in black, and the E3 ligase ligand is marked in blue.

PROTACs-targeting class IIa HDACs

Class IIa HDACs consist of HDAC4, HDAC5, HDAC7, and HDAC9, which play critical roles in regulating essential cellular metabolism and inflammatory pathways. Dissecting the specific roles of each class IIa HDAC isoform is hindered by the pan-inhibitory effect of current inhibitors and a lack of tools to probe their functions beyond epigenetic regulation [106]. In 2022, Macabuag et al. developed a novel series of HDAC4-selective PROTACs to investigate the role of HDAC4 in Huntington's disease (HD) pathology [107]. Two representative HDAC4 PROTAC **55** and **56** stood out as potent HDAC4 degraders. The TFMO-based PROTAC **56** showed about 8-fold more potent HDAC4 degradation than the HA-based PROTAC **55** in Jurkat E6-1 cells [107]. In 2024, Zhu's group reported a VHL-recruiting

PROTAC **57**, which selectively targets and degrades HDAC7, resulting in the effective attenuation of a specific set of proinflammatory cytokines in both lipopolysaccharide (LPS)-stimulated macrophages and a mouse model [106]. In a more recent effort, another selective HDAC7 PROTAC **58** was developed by Dong's group, which showed stronger antiproliferative effects than pan-class IIa inhibitor TMP269 in various diffuse large B cell lymphoma (DLBCL) and AML cells [108]. These studies unveil the deacetylase-independent functions of HDAC7 in inflammation and cancer and highlight its therapeutic potential as a promising target for the treatment of these diseases.

Table 2 Representative PROTACs targeting Class IIa HDACs with their degradation efficiencies and selectivity profiles

ID	Structures	Targets (Activities)	Ref.
55		HDAC4 (DC_{50} = 37 nM, D_{max} = 83%)	[107]
56		HDAC4 (DC_{50} = 4 nM, D_{max} = 78%)	[107]
57		HDAC7 (DC_{50} = 5 μM)	[106]
58		HDAC7 (90% degradation at 1 μM)	[108]

HDAC binder is marked in red, the linker is marked in black, and the E3 ligase ligand is marked in blue.

PROTACs-targeting class IIb HDACs

The class IIb HDAC family is composed of HDAC6 and HDAC10. Among all the HDACs, HDAC6 is the largest in size and the only one to contain two tandem catalytic domains and a C-terminal ubiquitin-binding zinc finger domain [1, 35]. HDAC10 is found in both the nucleus and cytoplasm and functions as a potent polyamine deacetylase with a notable preference for *N8*-acetylspermidine hydrolysis over acetylated lysine [1, 30]. Considering their important roles in the biological process related to various cancers and other diseases, they are emerging as promising therapeutic targets for the treatment of these diseases. In the past several years, some PROTACs-targeting class IIb HDACs, mainly HDAC6, have been developed. In 2018, the Tang group developed the first HDAC6

degrader **59** by connecting a non-selective HDAC inhibitor with an E3 ligase CRBN ligand [109]. PROTAC **59** selectively induced the degradation of HDAC6 in MCF-7 cells [109]. Later, they reported a new generation of HDAC6 degraders by tethering selective HDAC6 inhibitor Nexturastat A with CRBN ligand [110]. By varying the linker length and linking position, a potent HDAC6 degrader **60** with nanomolar DC_{50} value in MM1.S cells was identified and demonstrated more potent anti-proliferative activities against multiple myeloma (MM) cells than HDAC6 inhibitor [110]. However, the neo-substrates of CRBN, IKZF1, and IKZF3 were also degraded upon PROTAC **60** treatment [110]. Later, another series of HDAC6 PROTACs were reported, among which PROTAC **61** showed comparable HDAC6 degradation potency with PROTAC **60**, but did not show a significant impact on the levels of both IKZF1 and IKZF3 in MM1.S cells [111]. In the same year, they also reported a novel series of VHL-recruiting PROTACs that selectively degrade HDAC6 PROTAC **62** was identified as the most potent candidate among this class of HDAC6 degraders. Similar to PROTAC **61**, PROTAC **62** demonstrated potent and selective HDAC6 degradation without the degradation of IKZF1 and IKZF3 in MM1.S cells [112]. In 2019, the Rao group also reported a series of HDAC6-targeting PROTACs by introducing pomalidomide onto the end of the aliphatic chain of HDAC6 selective inhibitor Nexturastat A [113]. The representative PROTAC **63** induced significant degradation of HDAC6 in multiple cell lines, amongst, MM.1S cells exhibited the best sensitivity to **63** [113]. In the same year, they also reported another series of HDAC6-targeting PROTACs by introducing pomalidomide to the benzene ring of Nexturastat A [114]. PROTAC **64** exhibited comparably excellent degradation potency on different cell lines in contrast to the previously reported aliphatic-chain-introducing PROTAC **63** [114]. In 2022, the Hansen group reported two HDAC6 PROTACs [94]. The PROTAC **65** was based on an unselective SAHA-like HDAC ligand, while PROTAC **66** was derived from a selective HDAC6 binder. These two potent HDAC6 degraders were capable of degrading HDAC6 (DC_{50} = 3.5 nM and 19.4 nM, respectively) [94]. Notably, compound **66** did not display any antiproliferative activities against any tested leukemia cell line, whereas **65** exhibited IC_{50} values in the double-digit micromolar range in three of the AML cell lines, probably owing to off-target HDAC inhibition [94]. In the same year, they also developed the first non-hydroxamate selective HDAC6 degrader **67** based on a difluoromethyl-1,3,4-oxadiazole warhead as ZBG, which may avoid the mutagenic and genotoxic potential of hydroxamate-based HDAC6 degraders [115]. Additionally, they developed a potent degrader of both HDAC6 and HDAC10. Importantly, PROTAC **68** neither degraded HDAC1, 4, 8, nor induced histone H3 hyperacetylation. [116]. More recently, they also reported the first ethyl hydrazide-based HDAC6 PROTAC **69**, which selectively triggered HDAC6 degradation without significant impact on other HDAC isoforms. However, despite the potent HDAC6 degradation activity, **69** showed poor antiproliferative activity against MM.1S cells with an IC_{50} value over 50 μM [117].

Table 3 Representative PROTACs targeting Class IIb HDACs with their degradation efficiencies and selectivity profiles

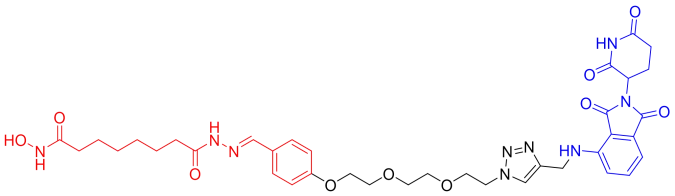
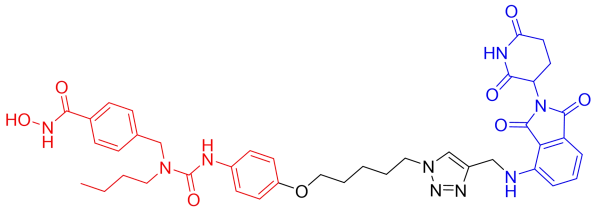
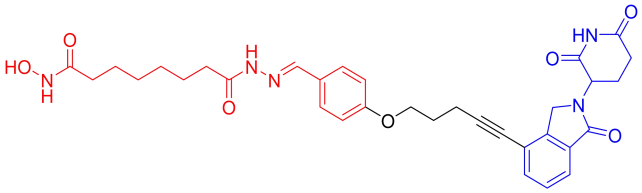
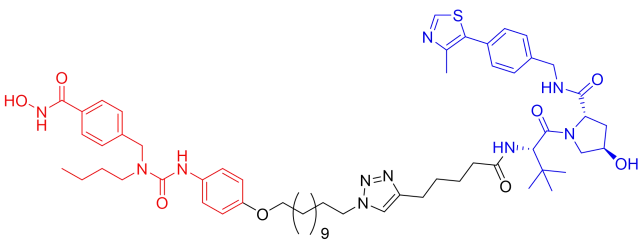
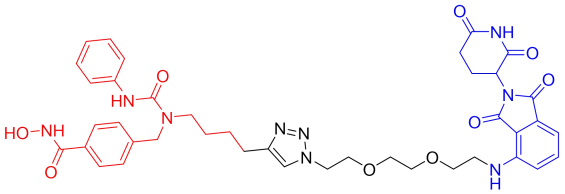
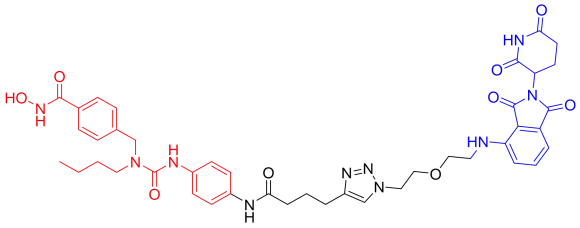
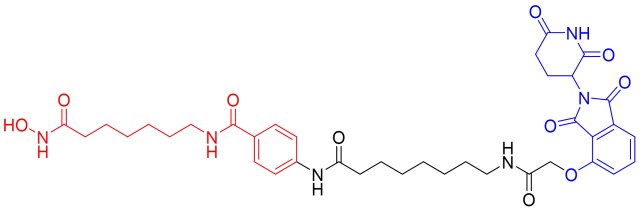
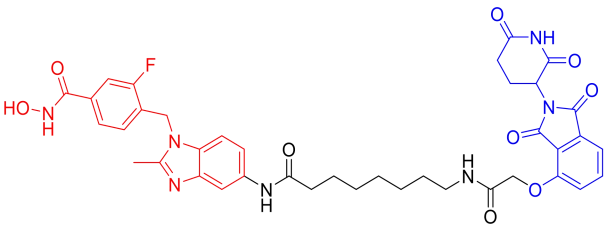
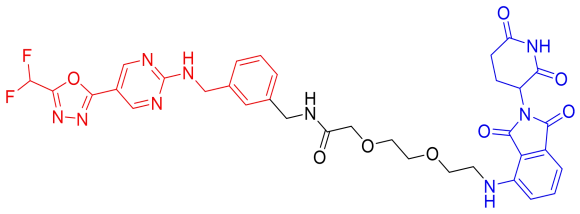
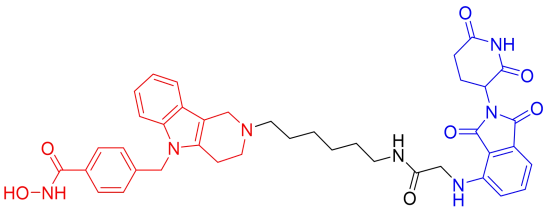
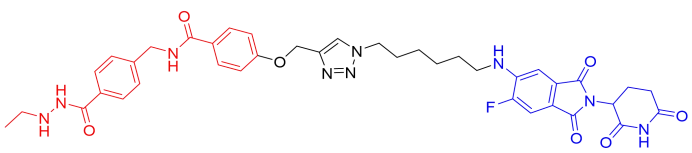
ID	Structures	Targets (Activities)	Ref.
59		HDAC6 (DC_{50} = 34 nM, D_{max} = 71%)	[109]
60		HDAC6 (DC_{50} = 1.6 nM, D_{max} = 86%)	[110]
61		HDAC6 (DC_{50} = 1.9 nM)	[111]
62		HDAC6 (DC_{50} = 11 nM, D_{max} = 89%)	[112]

Table 3 Representative PROTACs targeting Class IIb HDACs with their degradation efficiencies and selectivity profiles (*continued*)

ID	Structures	Targets (Activities)	Ref.
63		HDAC6 (DC_{50} = 3.8 nM)	[113]
64		HDAC6 (DC_{50} = 3.2 nM)	[114]
65		HDAC6 (DC_{50} = 3.5 nM, D_{max} = 84%)	[94]
66		HDAC6 (DC_{50} = 19 nM, D_{max} = 93%)	[94]
67		HDAC6 (DC_{50} = 131 nM, D_{max} = 84%)	[115]
68		HDAC6 (DC_{50} = 13 nM) HDAC10 (DC_{50} = 29 nM)	[116]
69		HDAC6 (DC_{50} = 14 nM, D_{max} = 91%)	[117]

HDAC binder is marked in red, the linker is marked in black, and the E3 ligase ligand is marked in blue.

Conclusion and perspectives

In the past several decades, development of HDAC inhibitors as therapeutic agents has made great progress, especially in oncology field. However, many challenges still remain in the clinical translation of HDAC inhibitors. In the review, we provided a summary of recently reported small molecule HDAC modulators. These small molecule HDAC modulators mainly include class-selective and isoform-selective HDAC inhibitors, slow-binding and covalent HDAC inhibitors, multi-target HDAC inhibitors, as well as HDAC PROTACs.

Although five HDAC inhibitors have gained approval for various cancer therapies, the approved HDAC inhibitors show low isoform selectivity, serious toxicity, unfavorable PK profiles, and poor efficacy against solid tumors. Many efforts have been made to develop isoform-selective HDAC inhibitors by using non-hydroxamate ZBGs, such as benzamide, trifluoromethyl ketone, alkyl hydrazides, and fluorinated oxadiazoles, and various structural modifications on the cap and linker, which might endow HDAC inhibitors with not only superior isoform/subclass selectivity but also better drug-likeness. However, some studies have demonstrated that targeting single HDAC isoforms, such as HDAC6, HDAC8, as well as HDAC10 hardly kills cancer cells directly although their oncological functions are well described [30, 35, 36, 118]. For instance, HDAC6 degrader **65** derived from a selective HDAC6 inhibitor capable of degrading HDAC6 with DC_{50} values of 19.4 nM did not display any inhibitory effects on the cellular viability of any tested leukemia cell line in the 0.5–50 μM concentration range [94]. Moreover, HDAC6 PROTAC **69** (DC_{50} = 14 nM, D_{max} = 91%) also showed poor antiproliferative activity against MM.1S cells with an IC_{50} value over 50 μM [117]. Similar results were also observed in HDAC8 PROTAC **53** whose antiproliferative activities, to a large extent, are due to off-target inhibition instead of HDAC8 degradation [104]. In addition, selective HDAC10 inhibition did not show potent antiproliferative activities [30], while targeting class I HDACs, especially HDAC1–3 showed excellent growth inhibition [54, 55, 119, 120], highlighting the important roles of HDAC1–3 in cancer cell survival. In addition, selective inhibition of class IIa HDACs via inhibitors did not provide profound antiproliferative activities, while selective HDAC7 degradation via PROTACs showed potent antiproliferative activities against hematologic malignancies [108]. These results indicate that isoform-selective HDAC inhibition may have a safer profile and indirect antitumor potential, such as antitumor immunomodulation. It is worth noting that HDAC inhibitors using these alternative ZBGs, such as benzamide and hydrazide, might be slow-binding inhibitors. It has been demonstrated that disregarding the slow-binding mechanism may misjudge not only the potency but also the isoform selectivity [121]. In addition to slow-binding reversible inhibitors, covalent HDAC inhibitors have also been developed to achieve irreversible target binding and durable therapeutic efficacy. The development of more drug-like covalent warheads/strategies and the identification of druggable amino residues should be the focus of this research field.

Compared with traditional HDAC inhibitors, multi-target HDAC inhibitors exhibit enhanced therapeutic efficacy against solid tumors by simultaneously blocking HDAC and resistant signaling pathways. Although a great number of multi-target HDAC inhibitors have been reported, these inhibitors also have several challenges, such as low selectivity, large size, poor cell permeability, unfavorable PK properties, imbalanced binding affinity, and safety concerns. Therefore, more efforts are required to develop improved multi-target HDAC inhibitors.

The development of HDAC PROTACs provided a strategy to explore the druggability of the non-enzymatic functions of HDACs. Currently, specific degradation of HDAC3, HDAC4, HDAC6, HDAC7, and HDAC8 have been achieved by PROTACs and most HDAC PROTACs were identified by western blot. However, no PROTACs targeting HDAC5, HDAC9, and HDAC11 have been reported yet. Recently, a molecule glue degrader, which can induce strong interactions between KBTBD4 and HDAC1/2 to promote corepressor degradation, was identified, providing an alternative strategy to target the HDAC complex [122, 123]. Most reported HDAC PROTACs recruit CRBN or VHL to induce HDAC degradation. However, CRBN and VHL-based PROTACs can also suffer from drug resistance [124]. Therefore, there is a need to hijack alternative E3 ligases, especially the tissue/cell or disease-specific E3 ligases, and develop novel screening methods, to develop the next generation of HDAC PROTACs with more drug-likeness.

Another challenge in the clinical translation of HDAC inhibitors is the complicated HDAC biology involved in cancer and other diseases. Further exploration the complicated HDAC biology (mainly including posttranslational modifications, epigenetic transcription regulation, and nonepigenetic cellular signaling cascades, mechanism of drug resistance, immunology) may help to reduce correlative cellular toxicity profiles and overcome drug resistance. In addition, identification of valid biomarkers of response also remains a significant challenge.

Although HDAC inhibitors can induce apoptosis and cell cycle arrest in cancer cells, their mechanisms of action remain elusive. Recently, several studies have demonstrated that HDAC inhibitors are capable of activating lipid peroxidation in certain cancer cells [104, 125, 126]. Interestingly, the various antiproliferative mechanisms of HDAC inhibitors are highly cell-type dependent [104]. In addition, combining HDAC inhibitors and ferroptosis inducers may help overcome drug resistance in certain types of cancers. Therefore, further efforts are also needed to explore the complicated biological roles of HDACs and their connection to different antiproliferative mechanisms in different cell types.

Besides traditional drug design, the application of artificial intelligence (AI) in drug design might also facilitate the discovery of novel HDAC modulators [127].

In conclusion, we provide a summary about the recent progress of small molecular HDAC modulators. We hope this review to be informative for developing the next generation of small molecular HDAC modulators, which can be not only potential therapeutics, but also valuable chemical tools to further explore the biological functions of HDACs.

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