

Current HDAC Inhibitors in Clinical Trials

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Abstract: Epigenetic modifications in eukaryotic biological pathways can lead to the up- or downregulation of regulatory proteins contributing to disease onset and progression. In the last three decades, histone deacetylases (HDACs) are among the most studied epigenetic targets. In fact, aberrant HDAC expression is associated with numerous types of cancer and neurodegenerative disorders, making HDACs promising molecular targets for the design of new drugs. Many HDAC inhibitors (HDACi) are currently in clinical evaluation for various types of cancer, and some of them have reached the market after approval by the Food and Drug Administration (FDA). The present review summarizes the various HDAC classes and relative isoforms. Then we discuss different classes or isoform-selective HDACi with a strong emphasis on late-stage preclinical candidates and drugs in clinical studies. Last but not least, we shed light on the pharmacokinetic challenges and future directions in HDACi design.

Keywords: Cancer · Clinical studies · Epigenetics · Histone deacetylases



Rossella Fioravanti graduated in Pharmacy at the Sapienza University of Rome in 1986. She is Associate Professor of Medicinal Chemistry in the Faculty of Pharmacy and Medicine, Sapienza University of Rome. She is the author of numerous publications; currently her research activity concerns the design, synthesis of molecules with heterocyclic structure, potential modulators of enzymes

(DNA methyltransferases, HDACs, histone methyltransferases/demethylases) involved in the epigenetic regulation of gene expression, and therefore potential new generation anticancer agents.



Antonello Mai obtained a degree in Pharmacy at Sapienza University of Rome, Italy, in 1984 and received his PhD in 1992 in Pharmaceutical Sciences at the same university. He is currently full Professor of Medicinal Chemistry at the Faculty of Pharmacy and Medicine, Sapienza University of Rome. His scientific oeuvre consists of more than 350 publications. His research is focused on the synthesis and

biological evaluation of new bioactive small-molecule epigenetic modulators but also of antibacterial, antiviral, and CNS agents.



Born in 1995, **Elisabetta Di Bello** is in the third year of her PhD course in Pharmaceutical Science, in the group of Prof. Antonello Mai. She graduated in October 2019 in Medicinal Chemistry and Technology, and still today, she has been involved in different projects, including the design and synthesis of potential inhibitors and/or activators of numerous epigenetic targets such as HDAC, SIRT, PRMT,

LSD1, and so on, implicated in cancer and neurodegenerative diseases.



Born in 1996, **Beatrice Noce** is in the first year of her PhD course in Pharmaceutical Science in the group of Prof. Antonello Mai. Currently she is carrying out the synthesis of small organic molecules for epigenetic (and not only) targets implicated in a large number of pathologies, in particular cancer and neurodegenerative diseases. She graduated in January 2021 in Medicinal Chemistry and Technology with a mark of 110 with honors.

1. Introduction

The definition of epigenetics can be formalized in “heritable alterations in gene expression that are not a result of alterations in underlying DNA sequence”.^[1] Lysine post-translational modifications (PTMs) are key players in epigenetic regulation of transcription and non-epigenetic cell signaling processes.^[2] In particular, acetylated lysines are the most studied PTMs. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are important post-transcriptional modifiers capable of regulating the protein acetylation and involved in several pathophysiological conditions.^[3] HATs catalyze the acetylation of amino-terminal lysine residues in histones using acetyl-coenzyme A (acetyl-CoA) as a donor of the acetyl moiety (Fig. 1). This covalent chemical modification leads to opening of the chromatin structure, recruitment of transcription factors and the RNA polymerase machinery, and activation of gene transcription. On the other hand, HDACs, with an opposite reaction, deacetylate the ϵ -NHCOCH₃ group of the acetyl-lysine residues on histone tails and close the chromatin structure through formation of ionic bonds between the positively charged free ammonium groups of the histone Lys side chains and the negatively charged DNA phosphate groups, leading to gene silencing.^[4] Since HDACs overexpression is implicated in the evolution of many diseases, researchers around the world are more and more interested in the development of new HDAC inhibitors.^[5]

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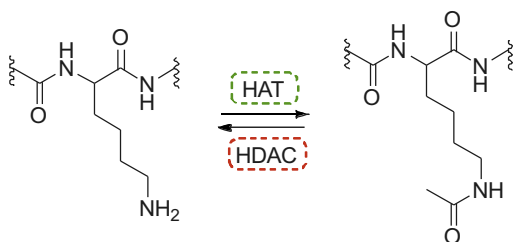


Fig. 1. Acetylation and deacetylation of the amino group at lysine residues on histone tails.

2. Human Classes of HDACs

In humans, there are eighteen different isoforms of HDACs divided into two families according to their characteristic catalytic mechanism.^[6] HDACs 1–11 are zinc-dependent metalloenzymes capable of hydrolyzing the amide bond using water as a nucleophile. Sirtuins 1–7 are the remaining seven deacetylases that depend on NAD⁺ as a cosubstrate for their function.^[7] Here we will describe in detail the eleven isoforms of the ‘classical’ HDACs, the zinc-dependent enzymes, distinguished into three classes: class I, comprising HDAC1-3,8, class II, split into two subclasses, IIa (involving HDAC4,5,7,9) and IIb (HDAC6,10), and class IV, containing HDAC11 as the only member so far. SIRT1-7 constitute the class III lysine deacetylases. The Zn²⁺ ion at the bottom of the HDAC catalytic pocket polarizes the carbonyl group of acetyl-lysine residues and stabilizes the acetylated substrate, thus facilitating the nucleophilic attack of the water molecules.^[8] In class I HDACs, although HDAC1 and HDAC2 have 80% sequence similarity, they develop independent roles in histone deacetylation. Cofactor and partner proteins are necessary for the action of HDAC1 and HDAC2: in fact, they only show activity within a complex of proteins essential for influencing their deacetylase activity and binding to DNA. Known protein complexes containing both HDAC1 and HDAC2 are Sin3, NuRD (nucleosome remodeling and deacetylating), and Co-REST.^[9] In addition to this, HDAC1 and HDAC2 activity regulation takes place *via* post-translational modifications, in particular phosphorylation. Hyperphosphorylation of HDAC1 and HDAC2 leads to increased deacetylase activity, while the opposite effect occurs with hypophosphorylation. So, phosphorylation is necessary to finetune HDAC1/2 activity.^[10]

HDAC3 is recruited by different multisubunit complexes, compared to other HDACs. Indeed, HDAC3 shares only 68% sequence homology with HDAC1 and HDAC2. Necessary co-repressors for HDAC3 activity are SMRT (Silencing Mediator for Retinoic acid and Thyroid hormone receptor) and N-CoR (Nuclear receptor Co-Repressor).^[11] HDAC3 is involved in the deacetylation of histone tails and, beyond the well-known role in embryonic development, it is also involved in several physiological processes (circadian rhythms, neuronal function, bone remodeling, and energy metabolism).^[12]

HDAC8 shares 34% similarity with HDAC1-3. Unlike the other class I HDACs, HDAC8 does not interact with cofactor proteins, but its activity is regulated by post-translational phosphorylation on S39. Moreover, it works independently and is smaller than the other isoforms.^[13] It can hydrolyze acyl-lysine peptides possessing acyl chains with a length of 2–16 carbons. To date, relatively few HDAC8 substrates are validated, as the main physiological function of HDAC8 is fatty acid deacetylation rather than deacetylation.^[14]

The class IIa deacetylases HDAC4, HDAC5, HDAC7, and HDAC9, are typically expressed in a tissue-specific way. The sub-cellular localization of HDAC4, HDAC5, HDAC7, and HDAC9 varies during the various steps of muscle cell differentiation. In

fact, these HDACs might be complementary to each other, controlling the gene expression during muscle cell differentiation.^[15] Muscles are not the only system regulated by these isoforms. In fact, they also modulate the physiology of the human cardiovascular, nervous, and immune systems.

HDAC6, belonging to the class IIb HDACs, resides predominantly in the cytoplasm. Its primary role is the tubulin deacetylation regulating microtubule-dependent cell mobility.^[16] Compared to the others, HDAC6 is the only isoform with two catalytic domains, CD1 and CD2. The first was believed to be inactive until recently, when CD1 was found to be a competent deacetylase with high substrate specificity (peptides containing C-terminal acetyl-lysine residues). CD2 possesses lysine deacetylase activity *in vitro*. HDAC6 is known to be highly involved in cancer and neurodegenerative diseases.^[17]

HDAC10, the second class IIb HDAC, has 37% similarity to HDAC6. This isoform, which is found in both the nucleus and cytoplasm, is an acetylpolyamine hydrolase that takes part in different processes such as immunoregulation, autophagy, or DNA repair.^[18]

The class IV HDAC11 is the smallest HDAC isoform and is a transcriptional regulator with a crucial function in immunomodulation. Similarly to HDAC8, this isoform prefers to hydrolyze acyl lysine residues with long chains, which can interact with a specific cavity of the enzyme.^[19]

3. HDAC Inhibitors Approved for Therapy and in Clinical Trials

A Zn²⁺ ion can be found at the bottom of the active site in most of the known HDAC isoforms. Such a catalytic tunnel is highly conserved across many species. Therefore, the developed HDACi possess a precise pharmacophore formed by a zinc-binding group (ZBG), crucial for the coordination of the catalytic zinc ion, a linker chain called hydrophobic spacer (HS), mimicking the lysine side-chain, a connecting unit (CU), that typically is represented by a carbonyl group as part of various chemical functionalities (ketone, amide, reverse amide, sulphonamide, carbamate, *etc.*) or by an heterocyclic ring, and a ‘cap’ group responsible for the interaction with the rim at the active site’s entrance.^[20] The general pharmacophore model of HDACi is depicted in Fig. 2.

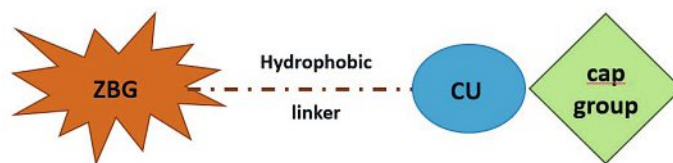


Fig. 2. Schematic representation of pharmacophore model for HDAC inhibitors. Fig. 2. Schematic representation of pharmacophore model for HDAC inhibitors.

The major classes of HDAC inhibitors comprise short-chain fatty acids, hydroxamic acids, benzamides (2'-aminoanilides), and cyclic peptides.^[21] Hydrazide-based HDAC inhibitors were also described.^[22] In the majority of HDACi, the ZBG are hydroxamates, anilides, or thiols, with strong chelating properties for the catalytic Zn²⁺ ion.

Hydroxamic acid-based and cyclic peptides HDACi were the first to be developed as anticancer agents. So far, five HDACi have been approved for cancer treatment by the US Food and Drug Administration (FDA): the first marketed HDAC inhibitor was Vorinostat (SAHA), a pan-HDACi developed by Merck, and the second one was the depsipeptide Romidepsin (FK228), a natural

product isolated from the bacterium *Chromobacterium violaceum*. Romidepsin is a class I-selective inhibitor able to treat refractory cutaneous T-cell lymphoma (CTCL) (Fig. 3).^[23] Panobinostat (LBH589, pan-HDACi) and Belinostat (PXD101, pan-HDACi) entered on the market upon FDA approval for patients with multiple myeloma (MM), cutaneous T-cell lymphoma, PTCL (peripheral T-cell lymphoma) (Fig. 3).^[24] The Chinese FDA (CFDA) approved Tucidinostat (chidamide), a 2'-aminoanilide active against HDAC1, -2, -3, -10, for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) (Fig. 3).^[25]

The history of the discovery and development of HDACi started from the characterization of the natural metabolite **Trichostatin A** (TSA, Fig. 4), which was the first potent HDAC inhibitor described by Yoshida *et al.* in 1990.^[26] TSA can be used as a perfect example of the HDAC pharmacophore model: the hydroxamic acid functions as a bidentate zinc chelator, the diene as a rigid linker, and the substituted phenyl ring as the cap group. TSA was the most known HDACi and one of the most used as a chemical probe to dissect physio- and pathological roles of HDACs in many different biological contexts. In 2006, Suberoylanilide hydroxamic acid (SAHA, Fig. 4), also known as **Vorinostat** (Zolinza[®]), was the first synthetic FDA-approved non-selective HDAC inhibitor used in the treatment of cutaneous T-cell lymphoma (CTCL).^[27] SAHA acts as a zinc chelator in the HDAC active site in a bidentate fashion.^[28] As shown in preclinical studies, SAHA reduced metastatic potential and proliferation of tumor cells *via* the induction of apoptosis and cell-cycle arrest. SAHA also sensitized tumor cells to chemotherapy and/or radiotherapy.^[29] Even if SAHA was the first approved, its metabolic and kinetic profiles *in vivo* are far from ideal.^[30] TSA and SAHA are substrate-competitive inhibitors of HDACs. Both compounds, in fact, insert their aliphatic chains into the tube-like hydrophobic portion of the pocket and mimic the lysine side chain of the natural substrate. The hydroxamic groups, instead, reach the polar bottom at the end of the tunnel, where they coordinate the zinc ion through the carbonyl and the hydroxyl groups. Additionally, hydroxamates can form hydrogen bonds with the charge-relay systems histidines/aspartates, and with the Tyr297 hydroxy group, with the consequent removal of the water molecule from the catalytic site and the block of the catalytic activity of the enzyme. The two aromatic portions (4-dimethylaminophenyl and phenyl groups of TSA and SAHA, respectively) interact at the pocket entrance and in an adjacent surface groove, resulting in a capping of the pocket (Fig. 4).

Three other cinnamyl hydroxamates, **Resminostat** (RAS2410)^[31] and the already cited Belinostat and Panobinostat, are in clinical trials for treatment of tumors. Resminostat is an orally available class I, Iib, and IV HDAC selective HDACi with a potent inhibition for HDAC1, HDAC3, and HDAC6, with IC₅₀ values in the nanomolar range (42.5, 50.1, 71.8 nM, respectively).^[31,32] It has been used in clinical trials, for example, to treat hepatocellular carcinoma and Hodgkin's lymphoma. Structurally, Belinostat and Panobinostat are similar to Resminostat and to

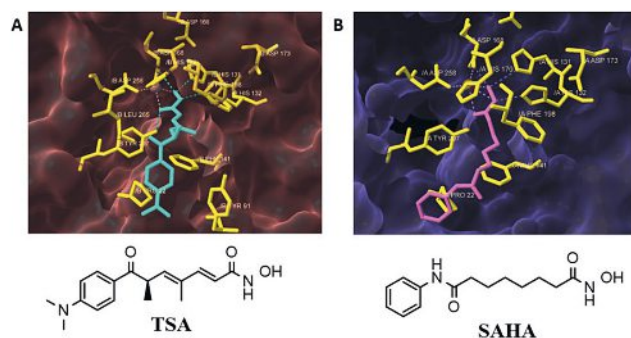


Fig. 4. A) Crystal structure of Trichostatin A (TSA) with HDLP (PMID: 1C3R); B) Crystal structure of Suberoylanilide hydroxamic acid (SAHA) with HDLP (PMID: 1C3S)

another clinical candidate, Pracinostat,^[33] since all these molecules contain a cinnamoyl linker replacing the polymethylene moiety of Vorinostat (Fig. 5). Generally, these cinnamates are characterized by a longer metabolic half-life, while the addition of a polar function in Pracinostat and Resminostat improves their oral bioavailability. **Panobinostat** (Farydak[®], Novartis) is a pan-deacetylase hydroxamic acid-based inhibitor approved for the treatment of adult patients with relapsed and/or refractory multiple myeloma (RRMM). These patients did not respond (anymore) to at least two previous therapies, such as by bortezomib or immunomodulatory agents. It is administered orally and has been formulated in capsules containing the active principle as a lactate salt.^[34] Panobinostat has been noted to play important apoptotic roles in cancer cells. Since Panobinostat monotherapy in people with RRMM has not shown sufficient activity, an attempt was made to switch to a combination therapy of HDACi with bortezomib and dexamethasone. The most prominent side effects of Panobinostat are diarrhea, fatigue, thrombocytopenia, asthenia, lymphopenia, and peripheral neuropathy.^[35] **Belinostat** (Beleodaq[®], TopoTarget) is a pan-deacetylase hydroxamate-based inhibitor approved for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL), a heterogenous non-Hodgkin Lymphoma, with poor outcomes.^[24b] Malignant T cells are particularly susceptible to the effects of this inhibitor as an accumulation of acetyl groups on histone tails causes cell cycle arrest and apoptotic cell death.^[12] It is present in lyophilized form for intravenous administration. The most common adverse reactions associated with Belinostat are nausea, vomiting, fatigue, pyrexia, and anemia in patients with PTCL. Beyond these, hepatotoxicity is undoubtedly the most serious side effect of Belinostat, not to be underestimated.^[36] Moreover, a series of compounds containing a rigid benzoylhydroxamic acid includes **Givinostat** (ITF2357)^[37] and **AR-42** (OSU-HDAC42) (Fig. 5).^[38] Structurally, these molecules are characterized by a more rigid benzoyl linker. Givinostat is a potent inhibitor of class I and II

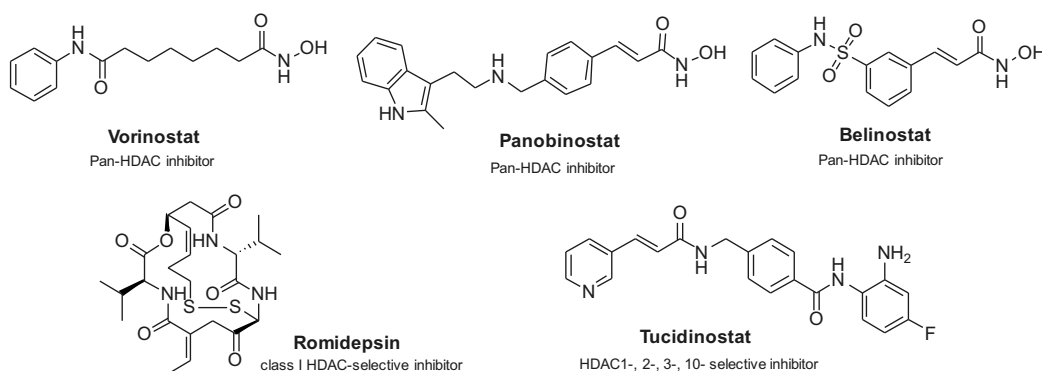


Fig. 3. Chemical structure of FDA-approved HDACi: Vorinostat, Romidepsin, Panobinostat, Belinostat. Chemical structure of the CFDA-approved HDACi: Tucidinostat.

HDACs – developed by Italfarmaco – approved with the status of orphan drug for the treatment of arthritis and polycythaemia, and currently in clinical trials for the treatment of Duchenne Muscular Dystrophy (DMD), juvenile idiopathic arthritis, polycythemia vera, and chronic myeloproliferative neoplasms.^[39] AR-42 is a nanomolar HDAC inhibitor ($IC_{50} = 16$ nM) related to hydroxamate-tethered phenylbutyrate.^[38,40] AR-42 has been evaluated in clinical trials to treat various diseases such as acoustic neuroma, intraocular lymphoma, meningioma, testicular lymphoma, and vestibular schwannoma, among others.^[41] **Romidepsin**, isolated from the bacterium *Chromobacterium violaceum*, is a bicyclic depsipeptide antibiotic with antineoplastic activity. Since thiols are not very stable and possess a poor bioavailability, the disulfide in Romidepsin resulted in higher stability and cell permeability.^[12] It is a prodrug, as in the target cells the disulfide is reduced to an active metabolite containing a thiol group able to chelate the zinc ions in the active site of the class I HDACs (Fig. 5).^[42] After intracellular activation, Romidepsin inhibits HDACs at low nanomolar level; in particular, it shows more selectivity for HDAC1 and HDAC2. This leads to alterations in gene expression and induction of cell cycle arrest, cell differentiation, and apoptosis. In phase II studies, Romidepsin produced a response in patients with relapsed or refractory CTCL and peripheral T-cell lymphoma (PTCL).^[43] **Entinostat** is a synthetic benzamide HDAC inhibitor showing selectivity against HDAC1 and HDAC3, with IC_{50} values of 0.3 and 8 μ M, respectively. Entinostat is an orally bioavailable drug; its most common adverse events include fatigue, gastrointestinal effects, hematologic and metabolic abnormalities.^[44] Entinostat has been studied in numerous phase I and II trials for solid and liquid tumors, including breast cancer.^[44] **Mocetinostat** is a 2'-aminoanilide HDAC inhibitor with potential antineoplastic activity, inhibiting specifically HDAC1,2. It possesses antitumor properties mainly in hematological tumors and much less in solid tumors, and it induces cell death, in part *via* mitochondrial pathway and *via* the destabilization of microtubules.^[45] The most common side effects are manageable such as fatigue, nausea, and vomiting.^[46] The orally bioavailable 2'-aminoanilide **Tucidinostat** (chidamide) was the first benzamide HDACi which reached the approval for clinical use (Fig. 5). It was approved by the CFDA in 2015 for the treatment of peripheral T-cell lymphoma.^[25] It inhibits

HDAC1, HDAC2, HDAC3, and HDAC10 with IC_{50} values of 95, 160, 67, and 78 nM, respectively.^[47] According to the crystal structure, this compound coordinates the zinc ion in a bidentate way, mainly *via* the amine group and much more weakly *via* the carbonyl oxygen. Compared to the hydroxamic acid HDACi, the benzamide derivatives are usually characterized by class I selectivity or individual HDAC isoform selectivity.^[48]

Currently, there are more than 20 HDACi in various stages of clinical evaluation, either as single agents or in combination with other chemotherapeutic agents or radiation therapy for the treatment of solid or liquid tumors. During the last few years, researchers in medicinal chemistry have significantly shifted the drug discovery paradigm from the 'one target-one drug' to the 'network active compound' approach, which is the cornerstone of modern polypharmacology.^[49] Multifactorial diseases such as cancer and neurodegenerative disorders could take great advantage by small molecules interacting at the same time with different dysregulated targets. Molecular microenvironments are complex, and their homeostasis depends on the correct interaction of genetic, epigenetic, and metabolic components at each time and in a given context.^[50] Therefore, it is intuitive that the traditional 'single-target' approach is often reductive, inadequate, and fraught with adverse side effects. Conversely, focusing on a holistic view of the disease and simultaneously targeting all the disease-relevant targets is currently considered an efficient strategy to achieve the desired full therapeutic effects.^[51] In this scenario, two distinct approaches are applied: i) Combination of two or more drugs acting on different targets; ii) Hybrid compounds containing in a single molecule two pharmacophore entities able to simultaneously modulate the activity of multiple targets.^[49c] So far, the combination of HDACi with other anticancer agents seems to be the most promising approach, which is largely investigated in preclinical and clinical settings as HDACi possess limited efficacy as a single treatment.^[49b,52]

4. Conclusion

Cancer is the most dreadful disease in which classical HDACs are involved.^[53] In addition, numerous evidences have highlighted that dysregulation of the balance between HDACs and HATs (especially CBP and p300) activities is responsible for synaptic

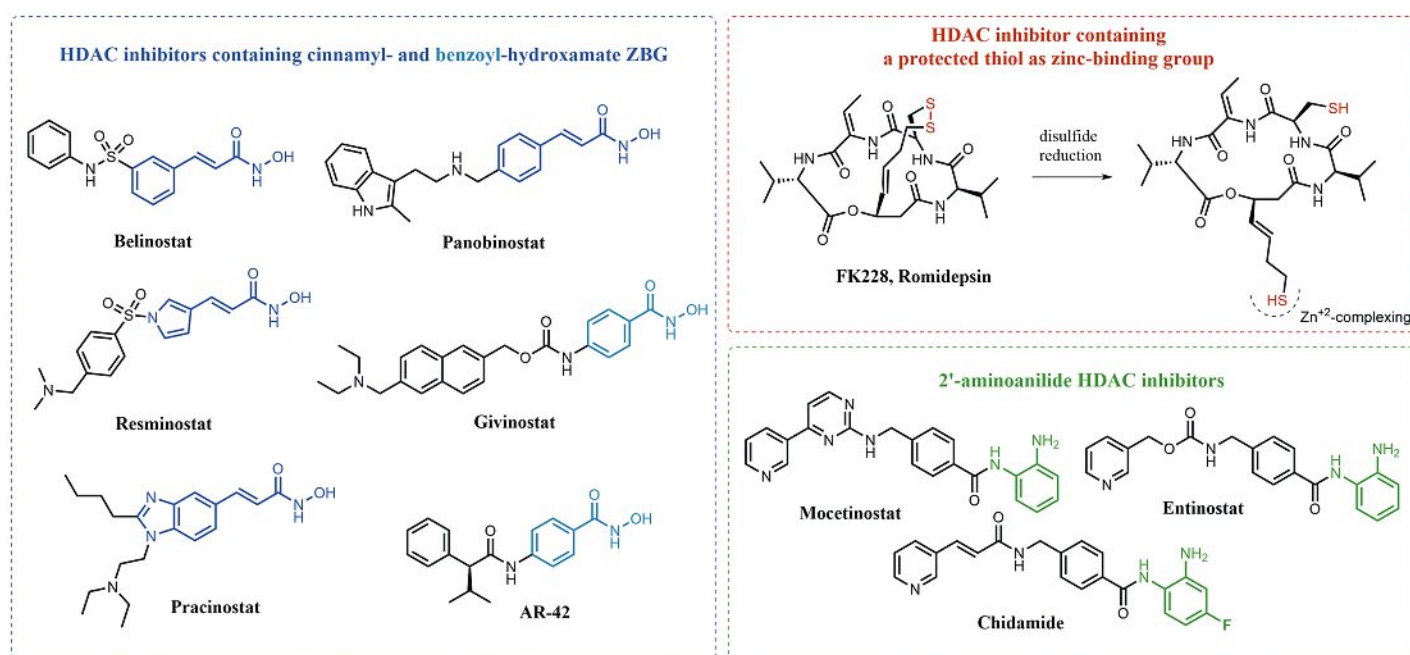


Fig. 5. HDAC inhibitors containing i) cinnamyl- (in blue) and benzoyl- (in light blue) hydroxamate ZBG, ii) protected thiol as ZBG, iii) 2'-aminoanilide HDAC inhibitors

plasticity and cognition disorders.^[54] Altered expression of different HDAC isoforms reported in literature has confirmed the active role of HDACs in modulating all the hallmarks of cancer as well as other diseases.^[55] Thus, the development of HDACi has been strongly sustained with the aim to elucidate the roles of HDACs in various pathological states in a deep and precise way and, therefore, to prove their efficacy.

So far, the FDA approved five HDACi for the treatment of hematological cancers only, since they possess poor efficacy in solid tumors as single agents. However, numerous clinical trials are currently demonstrating that the co-administration of HDACi together with other anticancer drugs or other chemotherapeutics can strongly improve the anticancer effects compared to monotherapy.^[49c] Cancer is a multifactorial disorder in which genetic and/or epigenetic alterations lead to deregulation and misregulation of numerous pathways involved in the onset and/or the progression,^[49a] thus the emerging novel therapeutic approach of polypharmacology could represent a real keystone for cancer therapy.^[49c]

Particularly, hybrid compounds incorporating two warheads in one single molecule, able to simultaneously inhibit two distinct cancer targets, allow to overcome some limits of the combination^[49c] drug metabolism, and drug–drug interactions. Moreover, these chimeric compounds guarantee in the same cells the simultaneous presence of both the pharmacologically active moieties.^[49c,56] This approach is still in its infancy and needs a multidisciplinary effort in the preclinical and clinical evaluation prior to arriving at the bedside of the patient. However, the first-in-class EGFR/HER2/HDAC hybrid inhibitor CUDC-101 entered clinical trials for cancer treatment, and showed increased apoptosis induction with respect to the combination of the single-targeting inhibitors, erlotinib (EGFR/HER2 inhibitor) and Vorinostat, in erlotinib-resistant tumor cells.^[49b]

Despite research efforts over the last 30 years, most HDACi currently in clinical trial evaluation have shown low selectivity between HDAC isoforms. Thus, given the specific roles of each HDAC isoform in cancer pathology, the development of isoform-selective inhibitors is still an important challenge for medicinal chemists, to enhance the potency of these compounds and overcome the problem of the side effects caused by the pan-HDAC inhibitors.

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