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# Current and Promising Histone Deacetylase Inhibitors in Cancer Therapy

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***Abstract:*** **Cancer is the most critical disease distressing humans and a primary cause of death on a global scale. Lately, the use of targeted anticancer medications as an approach for optimizing antitumor therapy has been urged. Changes in epigenetics in eukaryotic biological processes can result in the up- or downregulation of regulatory proteins contributing to disease onset and progression. Histone deacetylases (HDACs) have been one of the most researched epigenetic targets over the past three decades, also, HDAC enzymes are promising drug targets for the treatment of cancer. Truly, abnormal HDAC expression is associated with various kinds of cancer and neuro-degenerative disorders, establishing HDACs promising molecular targets for the design of new drugs. Numerous HDAC inhibitors (HDACIs) are currently in clinical evaluation for different forms of cancer, and some of them have reached the market following food and drug administration (FDA) approval. This review summarizes the various HDAC classes and discuss different classes HDACIs with a dedicated focus on late-stage preclinical candidates and drugs in clinical trials. Lastly, but just as importantly, we shed light on the future directions in HDACIs design which may help researchers in development and discovery of new horizons in cancer treatment.**

***Keywords:*** **Cancer, Clinical trials, Histone deacetylases, HDAC inhibitors.**

## 1. INTRODUCTION

In the current era of science and technology, cancer remains one of the most terrifying and incurable diseases in the world. It is a dark spot on the face of humanity as the second-leading cause of death and the leading cause among people younger than 85 years. In 2024, it is anticipated that there will be 2,001,140 new cases of cancer and 611,720 cancer-related deaths in the United States (1, 2). Regardless, the encouraging clinical progress of chemotherapeutic agents in cancer treatment and the development of new effective anticancer candidates still represent a challenging endeavor (3, 4). It is caused by genetic and/or epigenetic alterations leading to the dysregulation of different pathways through diverse molecular mechanisms (5). Despite significant advances in surgical, radiotherapeutic, and immunological approaches, which have improved cancer treatment outcomes, With 15 million deaths every year in 2030, according to the estimates, cancer has increased, raising an alarm as a real crisis for public health and health systems worldwide (6). Therefore, scientists began to introduce innovative solutions to control the global cancer health problem (7). Chemotherapy continues to be one of the most effective therapeutic strategies for treating hematological as well as solid tumors. Nevertheless, the clinical efficacy of drug therapy is often constrained by systemic toxicity, drug-resistance, and lack of selectiveness (8-10). Because of this dilemma, there is an urgent medical necessity to develop effective anticancer agents with an enhanced safety profile (11). Recently, there has been a growing interest towards targeting drug discovery to optimize antitumor therapies. One such target is histone deacetylase (HDAC), which is one of the most extensively, studied and established cancer targets (12).

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Since aberrant activity and overexpression of HDACs have been confirmed in a variety of cancer types, inhibiting HDACs has been proven to be an effective approach for developing HDACis as potential anti-cancer drugs (13). Notably, and during this short period, to date, six HDACis have been approved for the treatment of cutaneous T-cell lymphoma, involving vorinostat (SAHA), romidepsin, belinostat,panobinostat, chidamide, and pracinostat **(Figure 1)**. The currently effective histone deacetylase inhibitors (HDACis) are divided into four categories: (i) Carboxylates, short-chain fatty acids, including Valproic acid and Phenylbutyrate, (ii) hydroxamic acids or hydroxamates, such as Vorinostat, Panobinostat, and Belinostat; (iii) benzamides, such as Chidamide and Entinostat; and (iv) cyclic peptides, including depsipeptides and tetrapeptides (14).

Over the years, novel zinc-binding motifs have emerged and could provide complementary selectivity profiles or open the field to potentially new brain-penetrant HDACIs, in addition to the usual hydroxamic acid and o-aminoanilide ZBG-bearing HDACis, N-Alkyl hydrazides have transformed the field, providing innovative and practicalchemical tools for selective and effective inhibition of specific histone deacetylase (HDAC) enzymes(15).

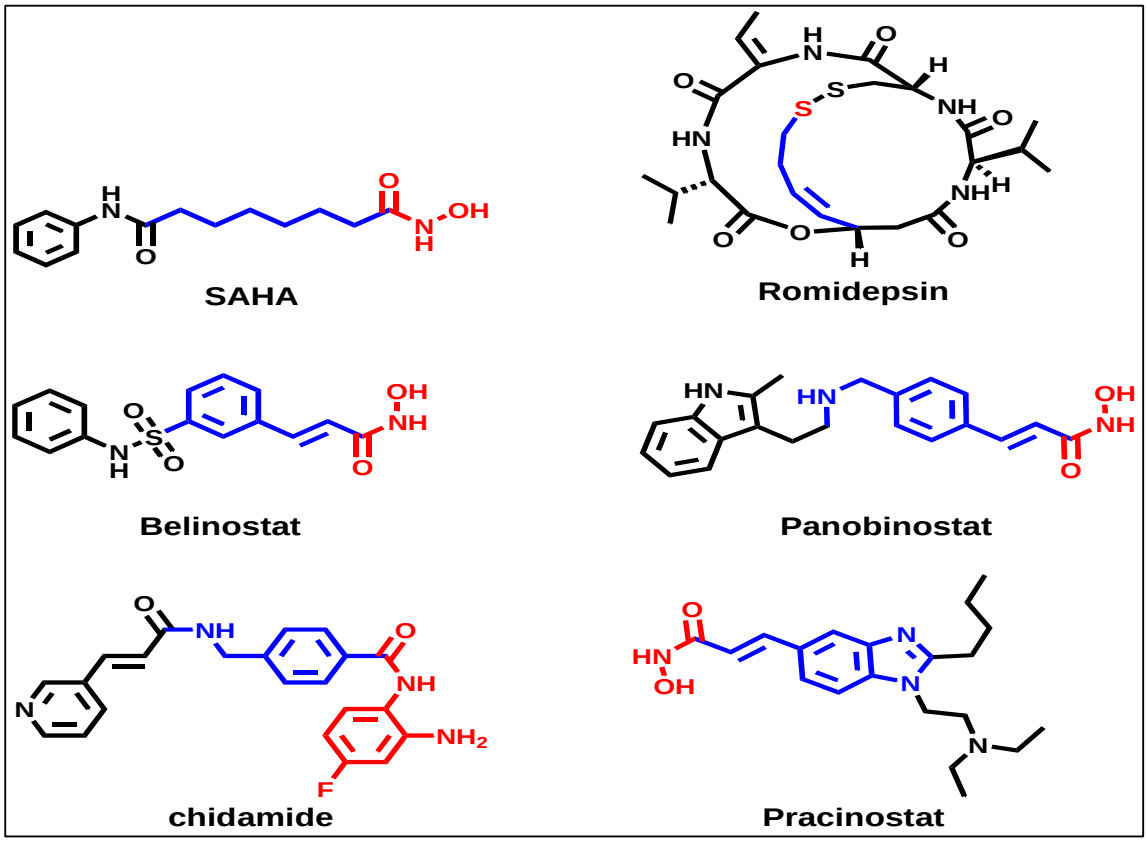


**Figure 1: HDAC inhibitors approved by the FDA.**

HDAC inhibitors can exhibit significant antiproliferative activity against cancer cells by blocking the cell cycle and inducing apoptosis. Recent studies showed that some class I HDAC inhibitor (SAHA) and HDAC3-selective inhibitors could augment antitumor immune responses by upregulating expression in tumour cells and enhancing immune cell infiltration(16).

## 2. HDACS AND CANCER

A number of factors influence gene expression and may thus modulate the complex process of cancer development. Long-term studies have focused on the genetic abnormalities of cancer-related genes but epigenetic modulation of gene expression is an essential regulatory process in cell biology (17) and growing evidence suggests that epigenetic regulation of genes also plays an important role during carcinogenesis (18, 19). Modifying DNA and/or histones can significantly alter gene expression, which is a possible explanation for the potential role of epigenetic regulation (18). HDAC is a broad group of important enzymes that catalyse the acetylation of histone and other intracellular substrates [62, 63]. It is self-evident and supported by evidence that HDAC dysregulation can result in a variety of tumor malignancies. As a result, HDAC enzymes

have become a popular target for developing novel anti-cancer drugs, and a novel group of anti-tumor medicines claimed as HDAC inhibitors has emerged as a result of their ability and potency to stop cell proliferation and maturation and induce programmed cell death [66, 67]. Dai *et al*. synthesized a number of SAHA derivatives using reversed amide linkers to improve SAHA and among these compounds, the indole-based compounds were of higher potency than other heteroaromatic derivatives [72]. Among these modifications, histone acetylation and deacetylation have vital functions in epigenetic regulation. There are more and more research results showing that HDACs expression was changed in a number of cancers. Further studies made out that the changes in the structure or expression of HDACs or HATs can irregulate gene transcription and cell signalling in cancer cells (20) **Figure 2**. The research results indicate that HDAC1 is increased in gastric cancer, oesophageal squamous cell carcinoma, hormone refractory prostate cancer (21), and also has a higher expression in colorectal cancer cells than in normal colon epithelial cells (22). HDAC2 and HDAC3 proteins are increased in colon cancer samples (23, 24). A truncating mutation of HDAC2 has been discovered in two colon cancer cell lines and two endometrial cancer cell lines (25). HDACs are engaged by oncogenic translocation protein complexes in different types of lymphomas and leukaemia (20, 26). However, there are also some studies that showed contradictory results. Most studies have shown that HDAC inhibitors can lead to cell cycle arrest and differentiation of many tumour cells *in vitro* and *in vivo* (27), but increased expression of HDAC1 enzymes were found showing better disease-free survival probability during a study of invasive breast cancer (28). Reduced expression of HDAC5 and HDAC10 is related to poor prognosis in lung cancer (29). All of these research results indicate that the mechanism of how these enzymes alter the gene transcription activities is complicated and hard to predict in any type of tumour cell and certain disease situation. It might have complex tissue-specific and tumour-specific expression patterns (27).

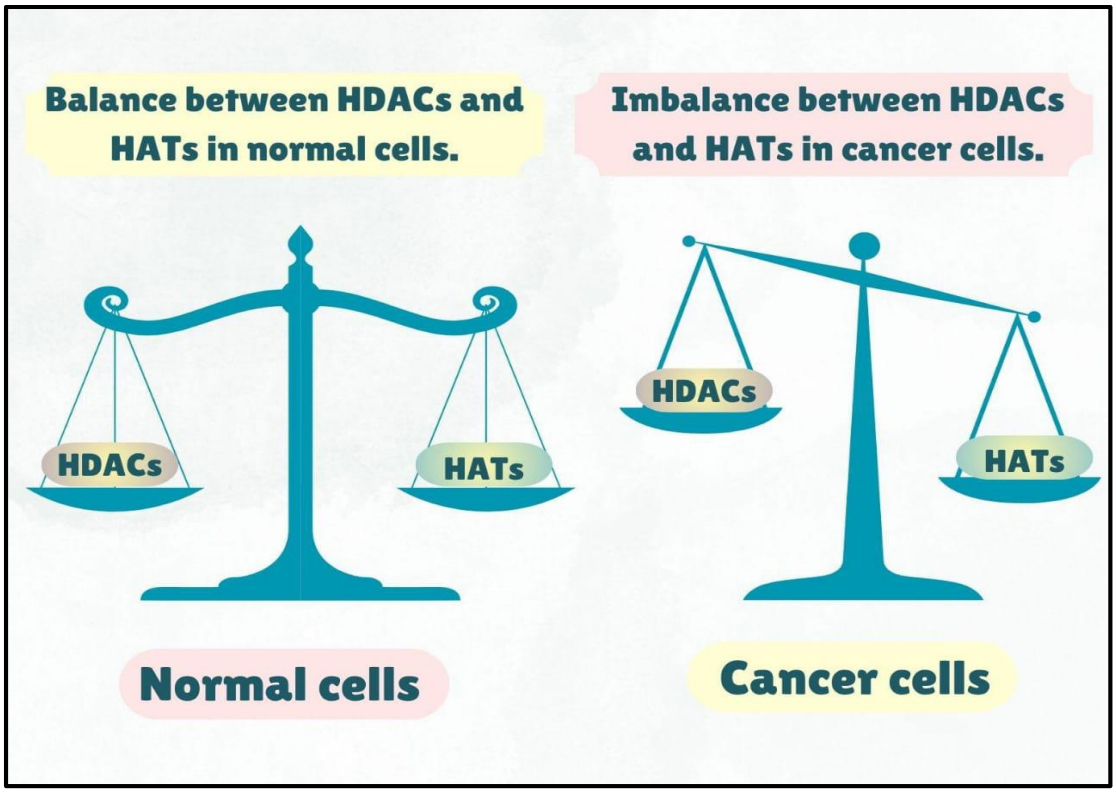


**Figure 2: Relation between HDACs & HATs in Normal *vs* cancer cells.**

The FDA approved HDACs inhibitors (HDACi) have been used for the treatment of hematological malignancies, and when used as a single therapeutic agent, they demonstrated a narrow therapeutic application mostly for the treatment of T cell lymphoma. Furthermore, resistance to HDAC inhibitors was often observed (30), though they remain poorly effective in solid tumors (31). Combining anticancer drugs with other chemotherapeutic agents usually led to maximize their efficacy, whilst reducing toxicity by administering lower drug doses. It also led to synergistic effects and contributed to the reduction in the potential for the development of resistance (32). Evidently, the concomitant and/or simultaneous co-administration of HDAC inhibitors with other anticancer agents can enhance anticancer effects and this stimulated the design of HDAC

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inhibitor-based hybrid candidates (33-36). Particularly, drug combinations have been sought to achieve improved efficacies, reduced or delayed development of drug resistance, decreased dosage, simultaneous enhancement of therapeutic actions, and decrease of side-effects (30, 31). HDAC inhibitors thereby offer an excellent prototypical system to explore and validate the multi-targeting hybrid drugs concept. In this review, an overview of the main HDAC inhibitors-based hybrids reported in the recent literature, including kinase inhibitors, epigenetic modulators, cytotoxic agents, hormone and vitamin D receptor modulators, natural products, and other anticancer drugs is summarized (35-39). In each study, the focus is on the strategy of the hybridization design as well as the important SARs and suggested the recommendation for future design and optimizations of similar hybrids.

### 2.1. Classes of histone deacetylases

The HDAC enzymes appear to be the major target of the histone deacetylase inhibitors (HDACIs). Until now, at least 18 human HDAC enzymes have been identified (27, 40) that are grouped into four main groups (41) based on their similarity to known yeast HDACs (20). HDAC1, HDAC2, HDAC3, and HDAC8 belong to class I, which is homologous to yeast RPD3. The enzymes of this group are mostly located in the nucleus of the cell. Class II relates to yeast HDA1 and is divided into the two sub-classes IIa and IIb. HDAC4, HDAC5, HDAC7, and HDAC9 belong to class IIa and are trafficking between nucleus and cytoplasm. Because of two catalytic sites, HDAC6 and HDAC10 are allocated to class IIb which they are mostly located in cytoplasm (20, 24). A conserved residue, which can be shared by class I and II, is found in the catalytic center of HDAC11 (42, 43) which is allocated to class IV and located both in nucleus and cytoplasm (44). There are another seven different HDACs with variable locations that are grouped to class III and yeast Sir2 (27).

#### 2.1.1.Mode of action of the HDAC enzymes

The mode of action of the HDAC enzymes involves removing the acetyl group from the histones comprising the nucleosome. Hypoacetylation results in a decrease in the space between the nucleosome and the DNA that is wrapped around it. Consequently, tighter wrapping of the DNA diminishes accessibility for transcription factors, leading to transcriptional repression (**Figure 3**) (45-47).

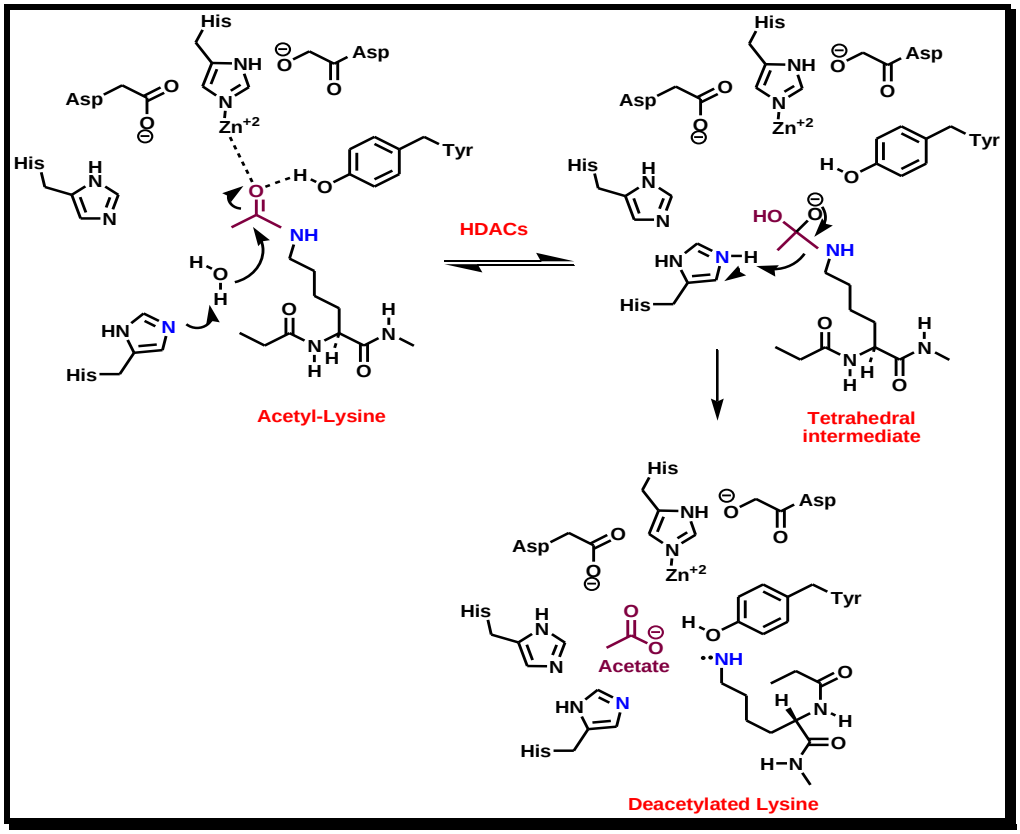


**Figure 3: Proposed chemical mode of class I/II/IV histone deacetylases (HDACs).**

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The catalytic domain of HDAC is formed by a stretch of ~ C390 amino acids consisting of a set of conserved amino acids. The active site consists of a gently curved tubular pocket with a wider bottom (48). Removal of an acetyl group occurs *via* a charge-relay system consisting of two adjacent histidine residues, two aspartic residues (located approx. 30 amino acids from the histidines and separated by approximately 6 amino acids), and one tyrosine residue (located approximately 123 amino acids downstream from the aspartic residues). An essential component of the charge-relay system is the presence of a $Zn^{2+}$ ion. This atom is bound to the zinc binding site on the bottom of the pocket (48, 49).

### 2.2. Histone deacetylase inhibitors (HDACIs)

In recent years, HDACIs have emerged as a promising new class of targeted anticancer agents, which are potent inducers of growth arrest, differentiation, and/or apoptotic cell death of transformed cells *in vitro* and *in vivo*. A large number of structurally diverse histone deacetylase inhibitors have been purified from natural sources or synthetically developed. These agents can generally be divided into seven classes based on their chemical structure. One of the most proven cancer targets is histone deacetylases (HDACs) (50). Histone deacetylase inhibitors (HDACIs) were developed as a result of the identification of abnormal activity of HDACs in a number of human malignancies (51, 52). The X-ray structure generally showed that HDACIs are made up of the following pharmacophores: The first one is the zinc-binding group (ZBG), which is responsible for coordinating the $Zn^{2+}$ at the bottom of the enzyme cavity**.** The second is the cap group (CAP), which facilitates interaction with the enzyme's catalytic tunnel rim. The third is the linker or hydrophobic spacer, which connects the cap moiety to the zinc-binding group, **Figure 4**.

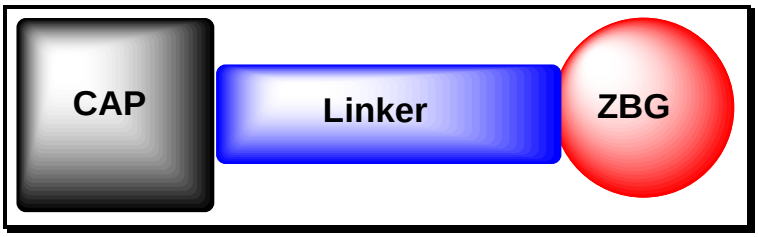


**Figure 4: General pharmacophore model of HDACIs.**

#### 2.2.1. Mechanism of action of HDACIs

HDACIs counteract the action of HDAC enzymes by two possible mechanisms; firstly, by promoting acetylation of histone which neutralizes the positive charge of the histone tails and reduces the affinity of histone for the negatively charged DNA. This loosens the structure of the chromatin to an open configuration which enables the transcriptional machinery to access the DNA and enhance gene transcription (**Figure 5**). Secondly, HDACIs promote acetylation of non-histone protein substrates (53, 54). These modifications of the non-histone proteins can affect many vital regulatory processes, including gene expression, mRNA stability, protein activity, and protein stability (55).

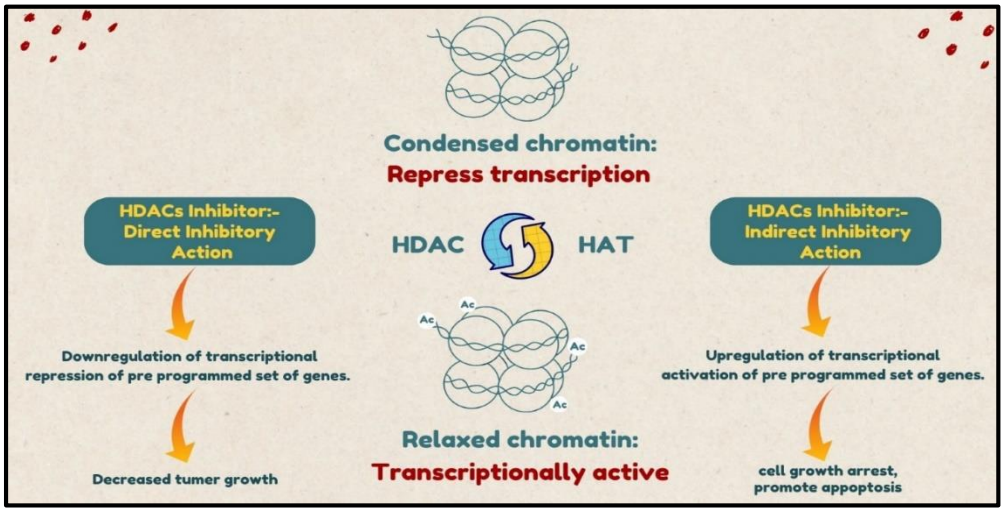


**Figure 5: Proposed mechanism of action of HDACIs.**

The effects of HDACIs on gene transcription are complex and involve multiple transcription factors and downstream alterations in gene expression. HDACIs induce a broad range of effects on cancer cells as illustrated in **Figure 6**, including cell cycle arrest, cell differentiation, production of reactive oxygen species, altered cell migration, autophagy, anti-angiogenic effects and induction of apoptosis in cancer cell lines in culture and *in vivo* including human bladder, breast, prostate, lung, ovary and colon cancer cells (20, 56-61). The cytotoxicity and more recently the DNA damaging effect of HDACIs is much more pronounced in malignant or transformed cells compared to normal cell lines (62).

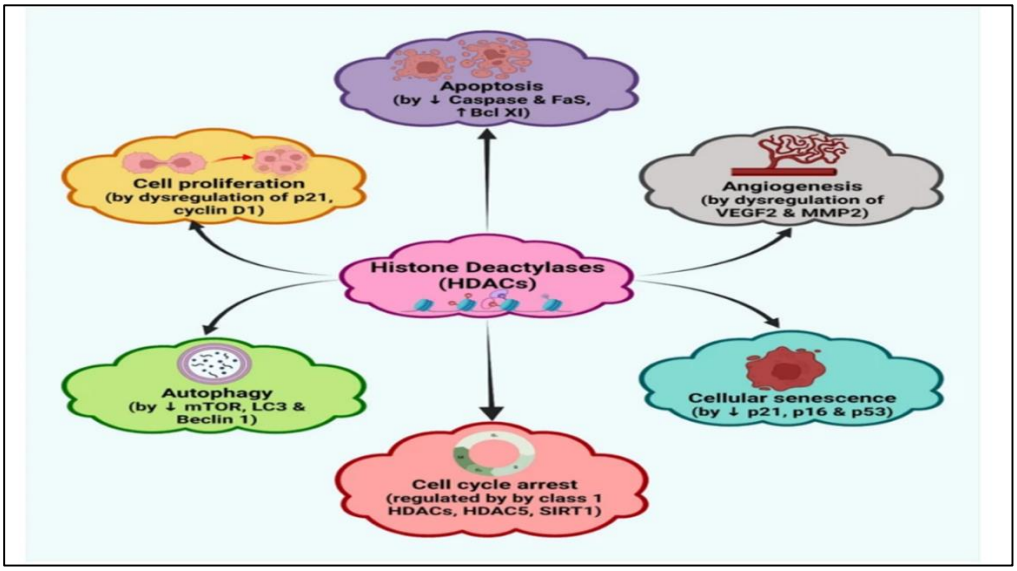


**Figure 6: Mechanisms of action of histone deacetylase inhibitors in cancer.**

### 2.2.2. Classes of histone deacetylase inhibitors

#### 2.2.2.1. Carboxylates

**Butyric acid**, a natural product generated in man by metabolism of fatty acids and bacterial fermentation of fiber in the colon, was the first identified HDACI from this class (63). The related compounds, such as **sodium phenyl acetate**, **sodium phenyl butyrate** and anticonvulsant **valproic acid** (64) were later found as antiproliferative agents, proved to be effective *in vivo* HDAC inhibitors and displayed marginal potency against solid tumors and leukemias (65). However, these carboxylates are far less potent in comparison with other inhibitors. The carboxylic acid chelating group is less active than the other functional groups such as hydroxamic acid; may be due to weak coordination with $Zn^{+2}$ ions. Despite, short chain fatty acids were extensively utilized as tools in clinicalresearch, reports on their activity continues to be very limited.


**Butyric acid** **sodium phenyl acetate** **sodium phenyl butyrate** **valproic acid**

#### 2.2.2.2. Hydroxamic acids

Hydroxamic acid derivatives are one of the well-studied ligand for the active site $Zn^{+2}$ of HDACs. They have constituted the broadest family of HDACIs. A large number of HDACIs containing hydroxamic acid as functional group are known, including natural products like trichostatin A (**TSA**). **TSA** was first isolated in 1976 by Tsuji *et al*., (66) from S*treptomyces hygrocopicus* as an fungistatic antibiotic active against *trichophytin* and the HDAC activity of **TSA** was found by Yoshida and co-workers in 1990 (67).The general structure of these inhibitors consists of a hydrophobic linker that allow the hydroxamic acid moiety to chelate the $Zn^{+2}$ cation at the bottom of HDAC catalytic pocket, while the bulky part of the molecule which is the surface recognition domain, acts as a cap group. The linker domain can consist of linear or cyclic structures, either saturated or unsaturated, is generally a hydrophobic group (**Figure 7**).

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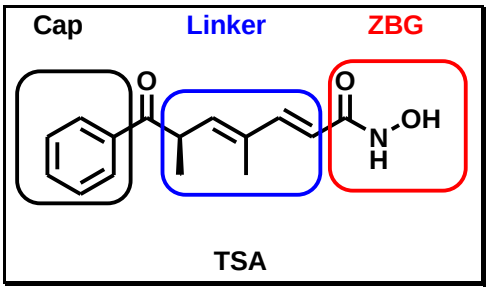
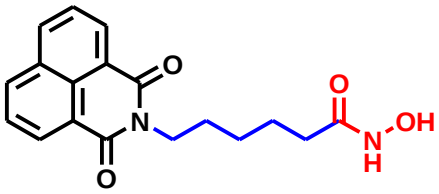



**Figure 7: Structural dissection of TSA based on crystal structure of HDLP-TSA complex.**

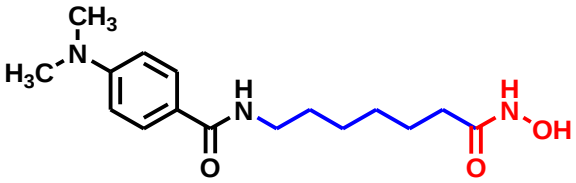
**TSA** is a potent inhibitor of HDACs with activity in the nanomolar concentrations, whereas the corresponding carboxylate, trichostatic acid, was shown to be ineffective as an HDACI, indicating that the hydroxamic acid is inevitable for the activity (68). Furthermore, the enantiomer (*S*)-TSA which was obtained by total synthesis, was demonstrated to be inactive (68, 69). The interactions of hydroxamic acid functional group at the active site of HDAC are known from the X-ray structure **(Figure 4)**. Based on the structure of **TSA** and its interaction with HDAC, a large number of HDACIs were designed and synthesized. Structurally simple **TSA** like straight chain hydroxamic acid, suberoylanilide hydroxamic acid (**SAHA**) **Figure 1,** was reported in 2006 by Breslow and co-workers, as a cytodifferentiating agent and HDACI (70, 71). **SAHA**, commercially known as vorinostat (Zolinza®), has the first synthetic FDA-approved non-selective HDAC inhibitor used in the treatment of cutaneous T-cell lymphoma (CTCL) (72). The synthetic **SAHA** and natural **TSA** which represent the archetypical hydroxamic acid HDACIs, have been instrumental in guiding the design of hydroxamic acid-derived HDACIs. After the disclosure of this potent synthetic compound, a large number of synthetic HDACIs were reported.

Kern and co-workers (73), *via* high-throughput transcriptional screening, identified **scriptaid** as a potent inhibitor of HDAC with $IC_{50}$ = 8.9 nM. On the other hand, Jung and co-workers synthesized reverse amide derivatives of TSA as HDACIs (74). These compounds were tested against both maize histone deacetylase (HD-2) and partially purified rat liver HDAC.

Variation in the substitution at the cap portion of the inhibitor and changing the spacer length enabled studying the inhibitory activity and the SAR of these compounds and they found that **M344 is** the most potent derivatives with HDAC1 $IC_{50}$ = 0.094 µM. This study confirmed the earlier observation that compounds with five and six methylene spacers are the most active (75). If the hydroxamic acid is changed to carboxylic acids, the activity of these amide analogues diminished.

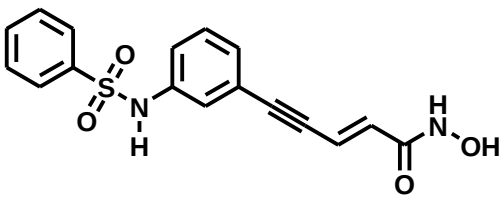



**Scriptaid**




**M344**

Moreover, Kim and co-workers reported another interesting compound, **oxamflatin**, containing a phenyl sulfonamide moiety as cap group with a spacer and hydroxamic acid functional group as ZBG (76). This compound was structurally different from other HDAC inhibitors and it was found to be a potent HDAC inhibitor of partially purified mouse HDAC ($IC_{50}$ = 15.7 nM), although it was found to be less potent than TSA ($IC_{50}$ = 1.44 nM) in the same assay.




**oxamflatin**

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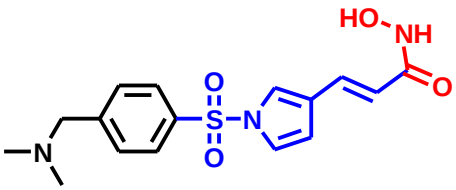
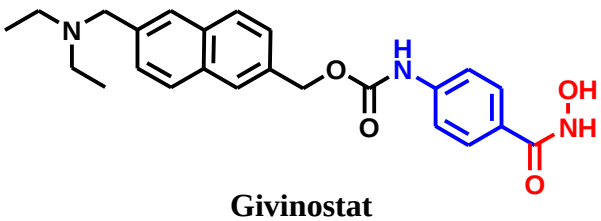
**Resminostat** (77), is an orally available class I, IIb, and IV HDAC selective HDACi with a potent inhibition for HDAC1, HDAC3, and HDAC6, with IC50 values in the nanomolar range (42.5, 50.1, 71.8 nM, respectively)(78). It has been used in clinical trials, for treatment of hepatocellular carcinoma and Hodgkin's lymphoma.



**Resminostat**

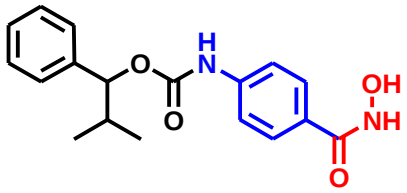
**Panobinostat** (Farydak®) (79) **Figure 1,** has been noted to play important apoptotic roles in cancer cells, is a pandeacetylase hydroxamic acid-based inhibitor approved for the treatment of adult patients with relapsed and/or refractory multiple myeloma (RRMM). These patients did not respond (anymore) to at least two previous therapies, such as by bortezomib or immune-modulatory agents. It is administered orally and has been formulated in capsules containing the active principle as a lactate salt(80). **Belinostat** (Beleodaq) (81) **Figure 1**, 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(82). It is found in lyophilized form for intravenous administration.

**Givinostat** (ITF2357) (15) is a potent inhibitor of class I and II HDACs – developed by Italfarmaco approved with the status of orphan drug for the treatment of arthritis and polycytaemia, and currently in clinical trials for the treatment of Duchenne Muscular Dystrophy (DMD), juvenile idiopathic arthritis, polycythemia vera, and chronic myeloproliferative neoplasms



**Givinostat**

**AR-42** is a nanomolar HDAC inhibitor ($IC_{50}$ = 16 nM) related to hydroxamate-tethered phenyl butyrate. **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 (83).



**AR-42**

#### 2.2.2.3. Benzamides or *ortho*-aminoanilides

Benzamides are the class of compounds which inhibit HDACs by ligating the active site $Zn^{+2}$ ion with a benzamide moiety. These compounds are generally less potent than the corresponding hydroxamic acid and cyclic tetrapeptide classes.

**Tucidinostat** (chidamide) (84) **Figure 1**, the orally bioavailable 2'-aminoanilide was the first benzamide HDACi which reached the approval for clinical use. It was approved by the CFDA in 2015 for the treatment of peripheral T-cell lymphoma. It inhibits HDAC1, HDAC2, HDAC3, and HDAC10 with $IC_{50}$ values of 95, 160, 67, and 78 nM, respectively. According to the crystal structure, this compound coordinates the zinc ion in a bidentate way, mainly *via* the amine group and much

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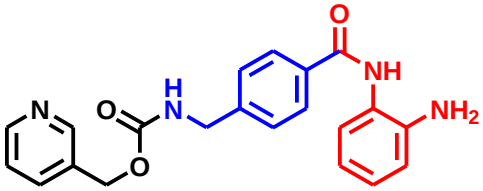
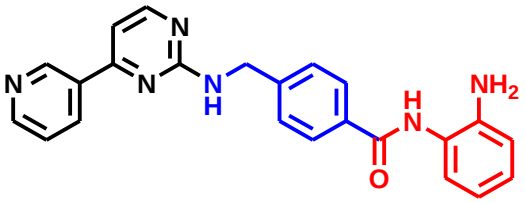
more weakly *via* the carbonyl oxygen. Compared to the hydroxamic acid HDACi, the benzamide derivatives are usually characterized by class I selectivity or individual HDAC isoform selectivity.

**Entinostat** (85), is a synthetic benzamide HDAC inhibitor showing selectivity against HDAC1 and HDAC3, with IC50 = 0.3 and 8 μM, respectively. Entinostat is an orally bioavailable drug; its most common adverse events include fatigue, gastrointestinal effects, hematologic and metabolic abnormalities. **Entinostat** has been studied in numerous phase I and II trials for solid and liquid tumors, including breast cancer.



**Entinostat**

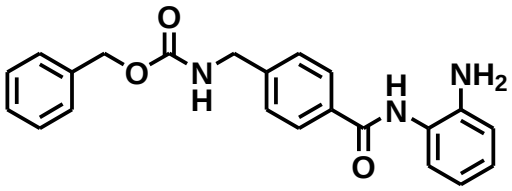
**Mocetinostat** (86), is HDAC inhibitor with potential antineoplastic activity, inhibiting specifically HDAC1,2. It possesses antitumor properties mainly in hematological tumors and much less in solid tumors, and it induces cell death, in part *via* mitochondrial pathway and *via* the destabilization of microtubules. The most common side effects are manageable such as fatigue, nausea, and vomiting.



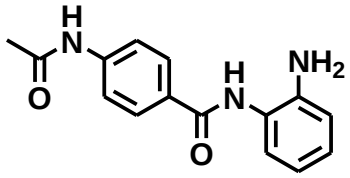
**Mocetinostat**

Suzuki and co-workers (87, 88) reported a series of synthetic benzamide-based non-hydroxamate HDAC inhibitors. **MS-275** is most potent compound of the series and now it is under clinical trials. It has HDAC inhibitory activity of 5 μM and showed significant anti-tumor activity *in vivo*. The SAR study of the benzanilide functionality revealed that a 2′-amino moiety is crucial for inhibitory activity against HDACs.

**CI-994**, which was investigated by Pfizer through phase II clinical studies as a single agent in oncology indications, is a subclass I-selective inhibiting HDACs 1, 2, and 3, with no significant inhibition of HDAC8 or the class IIa and IIb HDAC isoforms. Despite the fact that HDAC8 is a member of the class I HDACs, it is the least similar with only 30-34 % amino acid identity with HDACs1, 2, and 3.



**MS-275**



**CI-994**

Interestingly, Boissinot *et al*., (89) reported the discovery of **MI-192**, a selective HDAC2 and 3 inhibitor, obtained through modification of the surface-binding motif. **MI-192** displays high potency for HDACs 2 and 3 (30 nM and 16 nM, respectively), and excellent selectivity against all other isoforms (> 4 μM on HDACs 1, 4, 6, 7, and 8), although it is difficult to ascertain the origin of the observed isoform selectivity for HDACs 2 and 3 *vs* HDAC1. This is the first report describing a small molecule capable of imparting differential binding in favor of HDAC2 *vs* HDAC1.

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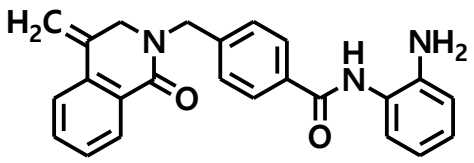
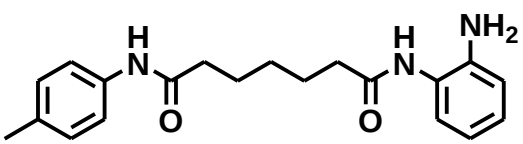
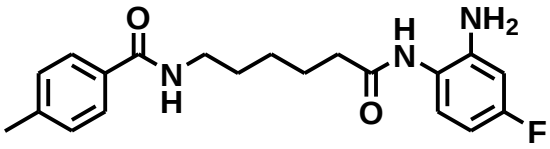


**MI-192**

Several groups have reported HDAC3-selective inhibitors within the *ortho*-aminoanilide family. Compounds **RGFP106,** and **RGFP136** (90) are *ortho*-aminoanilide HDAC3-selective inhibitors possessing a common saturated alkyl chain-linking motif. These studies demonstrate that it is possible to achieve selectivity for HDAC3 through careful choice of linker and surface-binding motifs coupled with the *ortho*-aminoanilide zinc-binding motif.



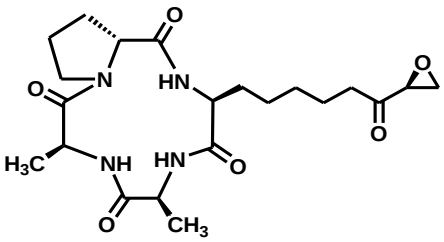
**RGFP106**



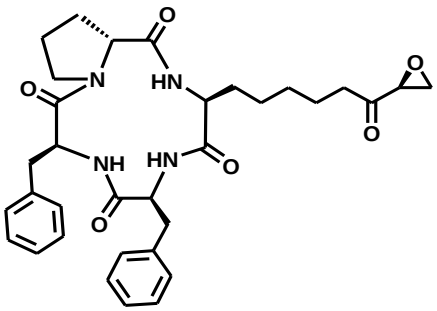
**RGFP136**

#### 2.2.2.4. Cyclic peptide inhibitors

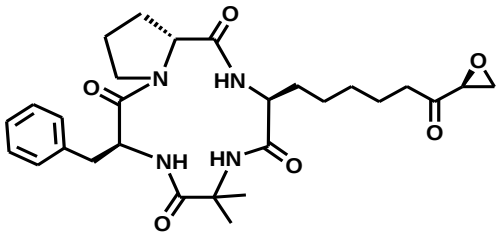
The first examples of the cyclic peptide class arose from screening natural products for antiparasitic or antiproliferation activity, with the Aoe-containing cyclic peptides being the first subclass isolated. These compounds include **HC-toxins** (91), **trapoxin B**(92), and **chlamydocin** (93).



HC-toxin



Trapoxin B



Chlamydocin A

**Romidepsin** (82)**Figure 1**, isolated from the bacterium *Chromobacterium violaceum*, is a bicyclic depsipeptide antibiotic with antiproliferative activity. Thiols are not very stable and possess a poor bioavailability, the disulfide in Romidepsin resulted in higher stability and cell permeability. 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. After intracellular activation, it inhibits HDACs at low nanomolar level; especially, 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, it produced a response in patients with relapsed or refractory CTCL and peripheral T-cell lymphoma (PTCL).

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#### 2.2.2.5. Other zinc-binding motifs

Recently, Whitehead *et al.*, (94) reported the discovery of a series of class I-selective inhibitors, exemplified by compound **1**, which uses an amino acid derivative as a zinc-binding motif. This structurally unique small molecule inhibitor showed preferential inhibition of HDAC8 ($IC_{50} = 90$ nM) *vs* all other HDACs (>18-fold selectivity over HDACs 1, 2, and 6). Wahhab *et al.*, (95) reported the use of a sulfamide moiety as a ZBG.

The potency and selectivity of the reported inhibitors, such as compound **2**, are believed to arise from the capping group linked to the ZBG by a long alkyl chain.

In 2013, compound **3**, with trifluoromethyloxadiazole group as a unique non-classical chelating ZBG, was reported as class IIa-selective HDACI (96). This structurally unprecedented HDACI exhibited good potency for the class IIa HDACs 4, 5, 7, and 9 (19–126 nM) and approximately 20-fold selectivity *vs* the class I HDACs. Moreover, Ononye *et al.*, (97) reported β-thujaplicin (a natural product from the tropolone family) derivatives with interesting HDAC isoform selectivity. While the tropolone functionality serves as the zinc-binding motif in compound **4**, the β-substituent (a cyclopentyl) presumably gives rise to its exquisite HDAC2 selectivity and potency (0.04 nM, > 3000-fold selectivity). This series of compounds represents the first report of highly potent and selective HDAC2 inhibitors. The β-substituted and O-methylated analog, compound **5**, is a highly potent and selective HDAC8 inhibitor (8 nM, > 1400-fold selectivity).

Etzkorn and co-workers (98) synthesized several phosphorous based SAHA analogues **6** and related compounds as HDACIs. However, these compounds showed very weak inhibitory activity during HDAC assays.

Jose *et al.*, synthesized a phosphonate **7** with a cap group of cyclic tetrapeptide and a spacer of five methylene units. The HDAC inhibitory activity study showed that this phosphonate compound **7** is a very weak HDACI. From all these phosphonate compounds studied for HDAC, it is clear that phosphonates are not good HDACIs, probably due to the high acidic nature of the phosphonate moiety, instead of the basic nature of the HDAC substrate (99).

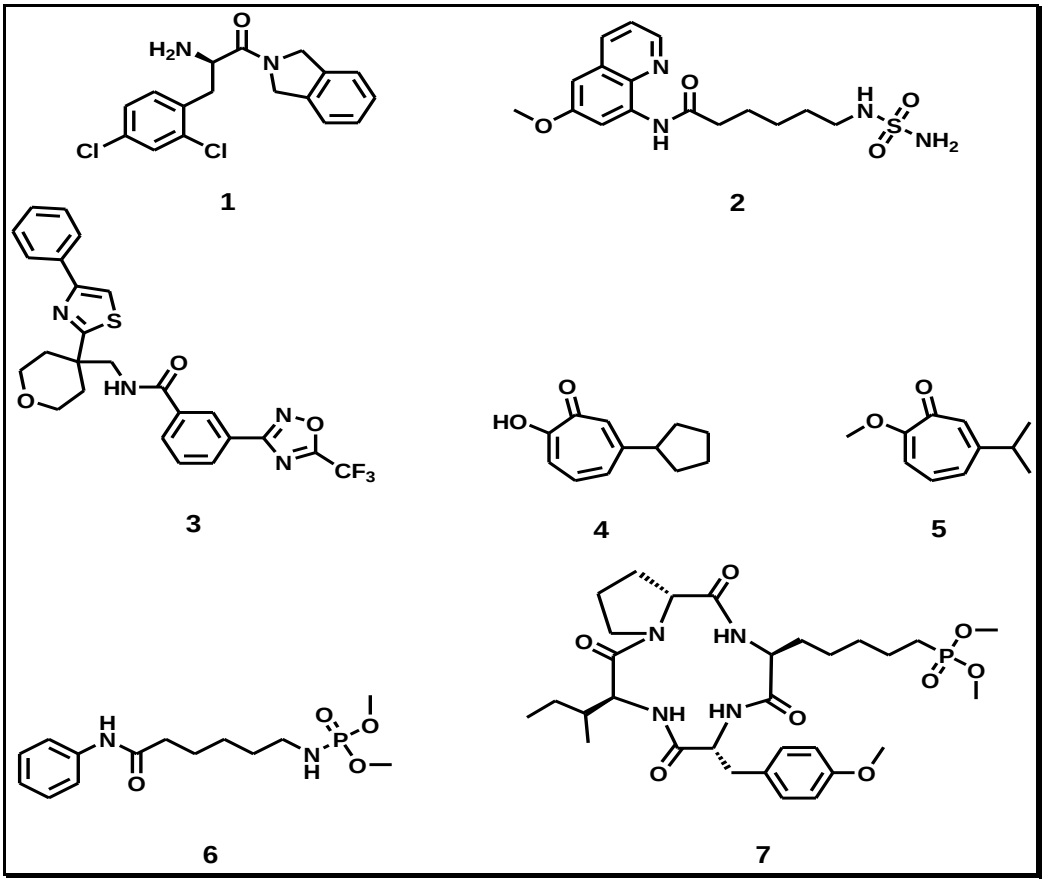


**Figure 8: Structural dissection of HDACIs bearing other zinc-binding motifs.**

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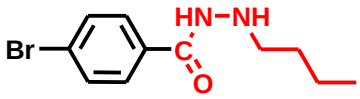
Hydrazides have emerged as a practical and effective alternative to the traditional hydroxamic acid ZBG-bearing HDACIs. N-alkyl hydrazides have significantly impacted the field of cancer treatment by introducing advanced chemical tools that can selectively and powerfully block specific HDAC enzymes. Liao and colleagues (100) identified hydrazide **UF010** as a new HDACI during a high-throughput screening process. The lead compound UF010 shows nanomolar activity on class I HDACs (HDAC1: $IC_{50}$ = 460 nM; HDAC2: $IC_{50}$ = 133 nM; HDAC3: $IC_{50}$ = 190 nM; HDAC8: IC50 = 2.83 μM) and is selective against other HDACs isoforms, class II b (HDAC6: $IC_{50}$ = 9.09 μM; HDAC10: $IC_{50}$ = 15.3 μM), as well as class IIa (HDAC4, 5, 7, 9: $IC_{50}$ > 100 μM).




**UF010**

## 3. CONCLUSION AND FUTURE DIRECTIONS

Cancer is the most awful disease in which classical HDACs are involved. HDACs are crucial for controlling chromatin structure and gene expression, making them attractive targets for cancer therapy. Presently, there are more than 20 HDACIs in various stages of clinical evaluation, either alone or in conjunction with radiation therapy or other chemotherapeutic medicines to treat liquid or solid malignancies. During the last few years, the "network active compound" method has substantially replaced the "one target-one drug" paradigm in drug development, according to medicinal chemistry researchers. Therefore, it is perceptive that the traditional 'single-target' approach is often reduced, insufficient, and delicate with adverse side effects. In the present 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 moieties able to concurrently modulate the activity of multiple targets. At this point, the combination of HDACIs with other anticancer agents seems to be the most promising approach, which is largely investigated in preclinical and clinical settings as HDACIs possess limited efficacy as a single treatment. Thus, numerous clinical trials are recently demonstrating that the co-administration of HDACIs together with other anticancer drugs or other chemotherapeutics can strongly improve the anticancer effects in comparison with monotherapy. So far, The majority of HDACi presently undergoing clinical trial review have demonstrated poor selectivity amongst HDAC isoforms, despite research efforts over the past 30 years. Therefore, the development of isoform-selective inhibitors remains a significant challenge for medicinal chemists in order to increase the potency of these compounds and solve the issue of the side effects caused by the pan-HDAC inhibitors, given the distinct roles that each HDAC isoform plays in cancer pathology.

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**Conflicts of interest declaration**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

## REFERENCES

[1] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA: a cancer journal for clinicians. 2024;74(1). doi: https://doi.org/10.3322/caac.21820.

[2] Ahmed AHH, Mohamed MFA, Allam RM, Nafady A, Mohamed SK, Gouda AE, et al. Design, synthesis, and molecular docking of novel pyrazole-chalcone analogs of lonazolac as 5-LOX, iNOS and tubulin polymerization inhibitors with potential anticancer and anti-inflammatory activities. Bioorganic Chemistry. 2022;129:106171. doi: https://doi.org/10.1016/j.bioorg.2022.106171.

[3] Thakur A, Tawa GJ, Henderson MJ, Danchik C, Liu S, Shah P, et al. Design, synthesis, and biological evaluation of quinazolin-4-one-based hydroxamic acids as dual PI3K/HDAC inhibitors. Journal of medicinal chemistry. 2020;63(8):4256-92. doi: https://doi.org/10.1021/acs.jmedchem.0c00193.

[4] Ibrahim TS, Sheha TA, Abo-Dya NE, AlAwadh MA, Alhakamy NA, Abdel-Samii ZK, et al. Design, synthesis and anticancer activity of novel valproic acid conjugates with improved histone deacetylase (HDAC) inhibitory activity. Bioorganic chemistry. 2020;99:103797. doi: https://doi.org/10.1016/j.cbpa.2019.03.002.

[5] Saini A, Kumar M, Bhatt S, Saini V, Malik A. Cancer causes and treatments. Int J Pharm Sci Res. 2020;11:3121-34.

[6] Stazi G, Fioravanti R, Mai A, Mattevi A, Valente S. Histone deacetylases as an epigenetic pillar for the development of hybrid inhibitors in cancer. Current opinion in chemical biology. 2019;50:89-100. doi: https://doi.org/ 10.1016/j.cbpa.2019.03.002.

[7] de Lera AR, Ganesan A. Epigenetic polypharmacology: from combination therapy to multitargeted drugs. Clinical epigenetics. 2016;8:1-21. doi: https://doi.org/10.1186/s13148-016-0271-9.

[8] Malviya R, Singh AK, Yadav D. Multi-Drug Resistance in Cancer: Understanding of Treatment Strategies. Multi-Drug Resistance in Cancer: Mechanism and Treatment Strategies. 2023:1. doi: https://doi.org/10.1002/ 9781394209866.ch1.

[9] Lu W, Wang F, Zhang T, Dong J, Gao H, Su P, et al. BMCL 2014;22(9):2707-13. doi: https://doi.org/ 10.1016/ j.bmc.2014.03.019.

[10] Mohamed MFA, Shaykoon MSA, Abdelrahman MH, Elsadek BEM, Aboraia AS, Abuo-Rahma GE-DAA. J Bioinorg Chem. 2017;72:32-41. doi: https://doi.org/10.1016/j.bioorg.2017.03.005.

[11] Petrella A, Fontanella B, Carratu A, Bizzarro V, Rodriquez M, Parente L. Histone deacetylase inhibitors in the treatment of hematological malignancies. Mini reviews in medicinal chemistry. 2011;11(6):519-27. doi: https://doi.org/10.2174/138955711795843347.

[12] Lu W, Wang F, Zhang T, Dong J, Gao H, Su P, et al. Search for novel histone deacetylase inhibitors. Part II: design and synthesis of novel isoferulic acid derivatives. Bioorg Med Chem. 2014;22(9):2707-13. Epub 2014/04/08. doi: S0968-0896(14)00192-8 [pii] 10.1016/j.bmc.2014.03.019. PubMed PMID: 24702857.

[13] Petrella A, Fontanella B, Carratu A, Bizzarro V, Rodriquez M, Parente L. Histone deacetylase inhibitors in the treatment of hematological malignancies. Mini Rev Med Chem. 2011;11(6):519-27. Epub 2011/05/13. doi: BSP/MRMC/ Epub/217 [pii]. PubMed PMID: 21561404.

[14] Nasrollahzadeh MS, Eskandarpour V, Maleki MF, Eisvand F, Mashreghi M, Hadizadeh F, et al. Design, synthesis and biological evaluation of novel imidazole-based benzamide and hydroxamic acid derivatives as potent histone deacetylase inhibitors and anticancer agents. 2024;1297:136951.

[15] Carreiras MdC, Marco-Contelles J. Hydrazides as Inhibitors of Histone Deacetylases. Journal of Medicinal Chemistry. 2024;67(16):13512-33. doi: https://doi.org/10.1021/acs.jmedchem.4c00541.

[16] Yuan D, Gao Y, Xia L, Liu H, Wu X, Ding X, et al. Discovery of novel biphenyl compounds bearing hydroxamic acid moiety as the first PD-L1/class I HDACs dual inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry. 2025;40(1):2461190. doi: https://doi.org/10.1080/14756366.2025.2461190.

[17] Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007;128(4):683-92. Epub 2007/02/27. doi: 10.1016/ j.cell.2007.01.029. PubMed PMID: 17320506.

[18] Smith LT, Otterson GA, Plass C. Unraveling the epigenetic code of cancer for therapy. Trends Genet. 2007; 23(9):449-56. Epub 2007/08/08. doi: 10.1016/j.tig.2007.07.005. PubMed PMID: 17681396.

[19] Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature. 1998;391(6669):806-11. Epub 1998/03/05. doi: 10.1038/35888. PubMed PMID: 9486653.

[20] Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res. 2007;5(10):981-9. Epub 2007/10/24. doi: 10.1158/1541-7786.mcr-07-0324. PubMed PMID: 17951399.

[21] Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. 2006;5(9):769-84. Epub 2006/09/07. doi: nrd2133 [pii] 10.1038/nrd2133. PubMed PMID: 16955068.

[22] Ishihama K, Yamakawa M, Semba S, Takeda H, Kawata S, Kimura S, et al. Expression of HDAC1 and CBP/p300 in human colorectal carcinomas. J Clin Pathol. 2007;60(11):1205-10. Epub 2007/08/28. doi: 10.1136/jcp.2005. 029165. PubMed PMID: 17720775; PubMed Central PMCID: PMC2095491.

[23] Marks P, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. Nat Rev Cancer. 2001;1(3):194-202. Epub 2002/03/21. doi: 10.1038/35106079. PubMed PMID: 11902574.

[24] Dokmanovic M, Marks PA. Prospects: histone deacetylase inhibitors. J Cell Biochem. 2005;96(2):293-304. Epub 2005/08/10. doi: 10.1002/jcb.20532. PubMed PMID: 16088937.

[25] Ropero S, Fraga MF, Ballestar E, Hamelin R, Yamamoto H, Boix-Chornet M, et al. A truncating mutation of HDAC2 in human cancers confers resistance to histone deacetylase inhibition. Nat Genet. 2006;38(5):566-9. Epub 2006/04/28. doi: 10.1038/ng1773. PubMed PMID: 16642021.

[26] Linggi BE, Brandt SJ, Sun ZW, Hiebert SW. Translating the histone code into leukemia. J Cell Biochem. 2005;96(5):938-50. Epub 2005/09/17. doi: 10.1002/jcb.20604. PubMed PMID: 16167339.

[27] Lane AA, Chabner BA. Histone deacetylase inhibitors in cancer therapy. J Clin Oncol. 2009;27(32):5459-68. Epub 2009/10/15. doi: 10.1200/jco.2009.22.1291. PubMed PMID: 19826124.

[28] Krusche CA, Wulfing P, Kersting C, Vloet A, Bocker W, Kiesel L, et al. Histone deacetylase-1 and -3 protein expression in human breast cancer: a tissue microarray analysis. Breast Cancer Res Treat. 2005;90(1):15-23. Epub 2005/03/17. doi: 10.1007/s10549-004-1668-2. PubMed PMID: 15770522.

[29] Osada H, Tatematsu Y, Saito H, Yatabe Y, Mitsudomi T, Takahashi T. Reduced expression of class II histone deacetylase genes is associated with poor prognosis in lung cancer patients. Int J Cancer. 2004;112(1):26-32. Epub 2004/08/12. doi: 10.1002/ijc.20395. PubMed PMID: 15305372.

[30] Lee JH, Choy ML, Marks PA. Mechanisms of resistance to histone deacetylase inhibitors. Advances in cancer research. 2012;116:39-86. Epub 2012/10/24. doi: 10.1016/b978-0-12-394387-3.00002-1. PubMed PMID: 23088868.

[31] Halsall JA, Turner BM. Histone deacetylase inhibitors for cancer therapy: An evolutionarily ancient resistance response may explain their limited success. BioEssays : news and reviews in molecular, cellular and developmental biology. 2016;38(11):1102-10. Epub 2016/10/27. doi: 10.1002/bies.201600070. PubMed PMID: 27717012; PubMed Central PMCID: PMCPmc5091640.

[32] Hamze A. How do we improve histone deacetylase inhibitor drug discovery? Expert opinion on drug discovery. 2020;15(5):527-9. Epub 2020/03/03. doi: 10.1080/17460441.2020.1736032. PubMed PMID: 32116055.

[33] de Lera AR, Ganesan A. Epigenetic polypharmacology: from combination therapy to multitargeted drugs. Clinical epigenetics. 2016;8:105. Epub 2016/10/19. doi: 10.1186/s13148-016-0271-9. PubMed PMID: 27752293; PubMed Central PMCID: PMCPmc5062873.

[34] Benedetti R, Conte M, Iside C, Altucci L. Epigenetic-based therapy: From single- to multi-target approaches. The international journal of biochemistry & cell biology. 2015;69:121-31. Epub 2015/10/24. doi: 10.1016/j.biocel. 2015.10.016. PubMed PMID: 26494003.

[35] Hesham HM, Lasheen DS, Abouzid KAM. Chimeric HDAC inhibitors: Comprehensive review on the HDAC-based strategies developed to combat cancer. Medicinal research reviews. 2018;38(6):2058-109. doi: 10.1002/med.21505. PubMed PMID: 29733427.

[36] Luan Y, Li J, Bernatchez JA, Li R. Kinase and Histone Deacetylase Hybrid Inhibitors for Cancer Therapy. Journal of medicinal chemistry. 2019;62(7):3171-83. doi: 10.1021/acs.jmedchem.8b00189. PubMed PMID: 30418766.

[37] Berube G. An overview of molecular hybrids in drug discovery. Expert opinion on drug discovery. 2016;11(3):281-305. doi: 10.1517/17460441.2016.1135125. PubMed PMID: 26727036.

[38] Fu RG, Sun Y, Sheng WB, Liao DF. Designing multi-targeted agents: An emerging anticancer drug discovery paradigm. European journal of medicinal chemistry. 2017;136:195-211. doi: 10.1016/j.ejmech.2017.05.016. PubMed PMID: 28494256.

[39] Liu T, Wan Y, Xiao Y, Xia C, Duan G. Dual-target inhibitors based on HDACs: Novel antitumor agents for cancer therapy. Journal of medicinal chemistry. 2020.

[40] Wang L, Li H, Ren Y, Zou S, Fang W, Jiang X, et al. Targeting HDAC with a novel inhibitor effectively reverses paclitaxel resistance in non-small cell lung cancer via multiple mechanisms. Cell Death Dis. 2016;7:e2063. Epub 2016/01/23. doi: cddis2015328 [pii] 10.1038/cddis.2015.328. PubMed PMID: 26794658.

[41] Lucio-Eterovic AK, Cortez MA, Valera ET, Motta FJ, Queiroz RG, Machado HR, et al. Differential expression of 12 histone deacetylase (HDAC) genes in astrocytomas and normal brain tissue: class II and IV are hypoexpressed in glioblastomas. BMC Cancer. 2008;8:243. Epub 2008/08/21. doi: 1471-2407-8-243 [pii] 10.1186/1471-2407-8-243. PubMed PMID: 18713462.

[42] Pan LN, Lu J, Huang B. HDAC inhibitors: a potential new category of anti-tumor agents. Cell Mol Immunol. 2007;4(5):337-43. Epub 2007/11/03. PubMed PMID: 17976313.

[43] Fischle W, Dequiedt F, Hendzel MJ, Guenther MG, Lazar MA, Voelter W, et al. Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR. Mol Cell. 2002;9(1):45-57. Epub 2002/01/24. PubMed PMID: 11804585.

[44] Glaser KB. HDAC inhibitors: clinical update and mechanism-based potential. Biochem Pharmacol. 2007;74(5):659-71. Epub 2007/05/15. doi: 10.1016/j.bcp.2007.04.007. PubMed PMID: 17498667.

[45] Wade PA. Transcriptional control at regulatory checkpoints by histone deacetylases: molecular connections between cancer and chromatin. Hum Mol Genet. 2001;10(7):693-8. Epub 2001/03/21. PubMed PMID: 11257101.

[46] Strahl BD, Allis CD. The language of covalent histone modifications. Nature. 2000;403(6765):41-5. Epub 2000/01/19. doi: 10.1038/47412. PubMed PMID: 10638745.

[47] Yoshida M, Furumai R, Nishiyama M, Komatsu Y, Nishino N, Horinouchi S. Histone deacetylase as a new target for cancer chemotherapy. Cancer Chemother Pharmacol. 2001;48 Suppl 1:S20-6. Epub 2001/10/06. PubMed PMID: 11587361.

[48] Finnin MS, Donigian JR, Cohen A, Richon VM, Rifkind RA, Marks PA, et al. Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors. Nature. 1999;401(6749):188-93. Epub 1999/09/18. doi: 10.1038/43710. PubMed PMID: 10490031.

[49] Buggy JJ, Sideris ML, Mak P, Lorimer DD, McIntosh B, Clark JM. Cloning and characterization of a novel human histone deacetylase, HDAC8. Biochem J. 2000;350 Pt 1:199-205. Epub 2000/08/06. PubMed PMID: 10926844.

[50] Frühauf A, Behringer M, Meyer-Almes F-J. Significance of five-membered heterocycles in human histone deacetylase inhibitors. Molecules. 2023;28(15):5686. doi: https://doi.org/10.3390/molecules28155686.

[51] Feng LS, Cheng JB, Su WQ, Li HZ, Xiao T, Chen DA, et al. Cinnamic acid hybrids as anticancer agents: A mini-review. Archiv der Pharmazie. 2022;355(7):2200052. doi: https://doi.org/10.1002/ardp.202200052.

[52] Belvedere R, Morretta E, Novizio N, Morello S, Bruno O, Brullo C, et al. The Pyrazolyl-Urea Gege3 Inhibits the Activity of ANXA1 in the angiogenesis induced by the pancreatic cancer derived EVs. Biomolecules. 2021;11(12):1758. doi: https://doi.org/10.3390/biom11121758.

[53] Ocker M. Deacetylase inhibitors - focus on non-histone targets and effects. World J Biol Chem. 2010;1(5):55-61. Epub 2011/05/05. doi: 10.4331/wjbc.v1.i5.55. PubMed PMID: 21540990.

[54] Glozak MA, Sengupta N, Zhang X, Seto E. Acetylation and deacetylation of non-histone proteins. Gene. 2005;363:15-23. Epub 2005/11/18. doi: S0378-1119(05)00572-X [pii] 10.1016/j.gene.2005.09.010. PubMed PMID: 16289629.

[55] Spange S, Wagner T, Heinzel T, Kramer OH. Acetylation of non-histone proteins modulates cellular signalling at multiple levels. Int J Biochem Cell Biol. 2009;41(1):185-98. Epub 2008/09/23. doi: S1357-2725(08)00347-6 [pii] 10.1016/j.biocel.2008.08.027. PubMed PMID: 18804549.

[56] Marks PA. The clinical development of histone deacetylase inhibitors as targeted anticancer drugs. Expert Opin Investig Drugs. 2010;19(9):1049-66. Epub 2010/08/07. doi: 10.1517/13543784.2010.510514. PubMed PMID: 20687783.

[57] Rasheed W, Bishton M, Johnstone RW, Prince HM. Histone deacetylase inhibitors in lymphoma and solid malignancies. Expert Rev Anticancer Ther. 2008;8(3):413-32. Epub 2008/03/28. doi: 10.1586/14737140.8.3.413. PubMed PMID: 18366289.

[58] Frew AJ, Johnstone RW, Bolden JE. Enhancing the apoptotic and therapeutic effects of HDAC inhibitors. Cancer Lett. 2009;280(2):125-33. Epub 2009/04/11. doi: S0304-3835(09)00132-3 [pii] 10.1016/j.canlet.2009.02.042. PubMed PMID: 19359091.

[59] Manzo F, Tambaro FP, Mai A, Altucci L. Histone acetyltransferase inhibitors and preclinical studies. Expert Opin Ther Pat. 2009;19(6):761-74. Epub 2009/05/29. doi: 10.1517/13543770902895727. PubMed PMID: 19473103.

[60] Marks PA, Richon VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. J Natl Cancer Inst. 2000;92(15):1210-6. Epub 2000/08/03. PubMed PMID: 10922406.

[61] Lakshmaiah KC, Jacob LA, Aparna S, Lokanatha D, Saldanha SC. Epigenetic therapy of cancer with histone deacetylase inhibitors. J Cancer Res Ther. 2014;10(3):469-78. Epub 2014/10/15. doi: JCanResTher_2014_10_3_469_137937 [pii] 10.4103/0973-1482.137937. PubMed PMID: 25313724.

[62] Lee JH, Choy ML, Ngo L, Foster SS, Marks PA. Histone deacetylase inhibitor induces DNA damage, which normal but not transformed cells can repair. Proc Natl Acad Sci U S A. 2010;107(33):14639-44. Epub 2010/08/04. doi: 1008522107 [pii] 10.1073/pnas.1008522107. PubMed PMID: 20679231.

[63] Boffa LC, Vidali G, Mann RS, Allfrey VG. Suppression of histone deacetylation in vivo and in vitro by sodium butyrate. J Biol Chem. 1978;253(10):3364-6. Epub 1978/05/25. PubMed PMID: 649576.

[64] Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem. 2001;276(39):36734-41. Epub 2001/07/27. doi: 10.1074/jbc.M101287200 M101287200 [pii]. PubMed PMID: 11473107.

[65] Saadh MJ, Allela OQB, Kareem RA, Sanghvi G, Menon SV, Sharma P, et al. From Gut to Brain: The Impact of Short-Chain Fatty Acids on Brain Cancer. NeuroMolecular Medicine. 2025;27(1):10. doi: https://doi.org/10.1007/s12017-025-08830-8.

[66] Tsuji N, Kobayashi M, Nagashima K, Wakisaka Y, Koizumi K. A new antifungal antibiotic, trichostatin. J Antibiot (Tokyo). 1976;29(1):1-6. Epub 1976/01/01. PubMed PMID: 931784.

[67] Yoshida M, Kijima M, Akita M, Beppu T. Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. J Biol Chem. 1990;265(28):17174-9. Epub 1990/10/05. PubMed PMID: 2211619.

[68] Yoshida M, Hoshikawa Y, Koseki K, Mori K, Beppu T. Structural specificity for biological activity of trichostatin A, a specific inhibitor of mammalian cell cycle with potent differentiation-inducing activity in Friend leukemia cells. J Antibiot (Tokyo). 1990;43(9):1101-6. Epub 1990/09/01. PubMed PMID: 2211374.

[69] Mori K, Koseki K. Tetrahedron. 1998(44):6013-20.

[70] Richon VM, Webb Y, Merger R, Sheppard T, Jursic B, Ngo L, et al. Second generation hybrid polar compounds are potent inducers of transformed cell differentiation. Proc Natl Acad Sci U S A. 1996;93(12):5705-8. Epub 1996/06/11. PubMed PMID: 8650156.

[71] Richon VM, Emiliani S, Verdin E, Webb Y, Breslow R, Rifkind RA, et al. A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. Proc Natl Acad Sci U S A. 1998;95(6):3003-7. Epub 1998/04/18. PubMed PMID: 9501205.

[72] Grant S, Easley C, Kirkpatrick P. Vorinostat. Nat Rev Drug Discov. 2007;6(1):21-2. Epub 2007/02/03. doi: 10.1038/nrd2227. PubMed PMID: 17269160.

[73] Su GH, Sohn TA, Ryu B, Kern SE. A novel histone deacetylase inhibitor identified by high-throughput transcriptional screening of a compound library. Cancer Res. 2000;60(12):3137-42. Epub 2000/06/24. PubMed PMID: 10866300.

[74] Jung M, Brosch G, Kolle D, Scherf H, Gerhauser C, Loidl P. Amide analogues of trichostatin A as inhibitors of histone deacetylase and inducers of terminal cell differentiation. J Med Chem. 1999;42(22):4669-79. Epub 1999/12/02. doi: jm991091h [pii]. PubMed PMID: 10579829.

[75] Breslow R, Marks PA, Rifkind R. Potent inducers of terminal differentiation and methods of use thereof. . US Patent 5,700,811. 1997.

[76] Kim YB, Lee KH, Sugita K, Yoshida M, Horinouchi S. Oxamflatin is a novel antitumor compound that inhibits mammalian histone deacetylase. Oncogene. 1999;18(15):2461-70. Epub 1999/05/06. doi: 10.1038/sj.onc.1202564. PubMed PMID: 10229197.

[77] Raucci A, Castiello C, Mai A, Zwergel C, Valente S. Heterocycles–Containing HDAC Inhibitors Active in Cancer: An Overview of the Last Fifteen Years. ChemMedChem. 2024;19(18):e202400194. doi: https://doi.org/10.1002/cmdc.202400194.

[78] Zheng J, Wang S, Xia L, Sun Z, Chan KM, Bernards R, et al. Hepatocellular carcinoma: signaling pathways and therapeutic advances. Signal Transduction and Targeted Therapy. 2025;10(1):35. doi: https://doi.org/10.1038/s41392-024-02075-w.

[79] Ling L, Kim M, Soper A, Kovarova M, Spagnuolo RA, Begum N, et al. Analysis of the effect of HDAC inhibitors on the formation of the HIV reservoir. Mbio. 2024;15(9):e01632-24. doi: https://doi.org/10.1128/mbio.01632-24.

[80] Novotny-Diermayr V, Sangthongpitag K, Hu CY, Wu X, Sausgruber N, Yeo P, et al. SB939, a novel potent and orally active histone deacetylase inhibitor with high tumor exposure and efficacy in mouse models of colorectal cancer. Molecular cancer therapeutics. 2010;9(3):642-52. doi: https://doi.org/10.1158/1535-7163.mct-09-0689.

[81] Wang J, Zhou C, Li B, Liu H, Zhang H, Liu L. Design, synthesis, and in vitro biological evaluation of novel HDAC inhibitors bearing C-1 phenyl substituted tetrahydroisoquinoline Cap moiety as anti-tumor therapeutic agents. Medicinal Chemistry Research. 2024;33(4):687-702. doi: https://doi.org/10.1007/s00044-024-03206-2.

[82] Ho TCS, Chan AHY, Ganesan A. Thirty years of HDAC inhibitors: 2020 insight and hindsight. Journal of medicinal chemistry. 2020;63(21):12460-84. doi: https://doi.org/10.1021/acs.jmedchem.0c00830.

[83] Collier KA, Valencia H, Newton H, Hade EM, Sborov DW, Cavaliere R, et al. A phase 1 trial of the histone deacetylase inhibitor AR-42 in patients with neurofibromatosis type 2-associated tumors and advanced solid malignancies. Cancer chemotherapy and pharmacology. 2021;87:599-611. doi: https://doi.org/10.1007/s00280-020-04229-3.

[84] Huang H, Deng T, Qian J, Hu J, Zhu Y, Tian M, et al. Chidamide modulates proliferation, migration and apoptosis of human tongue squamous carcinoma SCC9 cells through multiple signaling pathways. Archives of Biological Sciences. 2021;73(3):415-23. doi: https://doi.org/10.2298/abs210815035h.

[85] Connolly RM, Rudek MA, Piekarz R. Entinostat: a promising treatment option for patients with advanced breast cancer. Future oncology. 2017;13(13):1137-48. doi: https://doi.org/10.2217/fon-2016-0526.

[86] Patel P, Wahan SK, Vishakha S, Kurmi BD, Gupta GD, Rajak H, et al. Recent progress in histone deacetylase (HDAC) 1 inhibitors as anticancer agent. Current Cancer Drug Targets. 2023;23(1):47-70. doi: https://doi.org/10.2174/1568009622666220624090542.

[87] inhibitory activity of new benzamide derivatives. J Med Chem. 1999;42(15):3001-3. Epub 1999/07/30. doi: 10.1021/jm980565u jm980565u [pii]. PubMed PMID: 10425110.

[88] Saito A, Yamashita T, Mariko Y, Nosaka Y, Tsuchiya K, Ando T, et al. A synthetic inhibitor of histone deacetylase, MS-27-275, with marked in vivo antitumor activity against human tumors. Proc Natl Acad Sci USA. 1999;96(8):4592-7. Epub 1999/04/14. PubMed PMID: 10200307.

[89] Boissinot M, Inman M, Hempshall A, James SR, Gill JH, Selby P, et al. Induction of differentiation and apoptosis in leukaemic cell lines by the novel benzamide family histone deacetylase 2 and 3 inhibitor MI-192. Leuk Res.36(10):1304-10. Epub 2012/07/24. doi: S0145-2126(12)00289-5 [pii] 10.1016/j.leukres.2012.07.002. PubMed PMID: 22818799.

[90] Rai M, Soragni E, Chou CJ, Barnes G, Jones S, Rusche JR, et al. Two new pimelic diphenylamide HDAC inhibitors induce sustained frataxin upregulation in cells from Friedreich's ataxia patients and in a mouse model. PLoS One. 2010;5(1):e8825. Epub 2010/01/26. doi: 10.1371/journal.pone.0008825. PubMed PMID: 20098685.

[91] Brosch G, Ransom R, Lechner T, Walton JD, Loidl P. Inhibition of maize histone deacetylases by HC toxin, the host-selective toxin of Cochliobolus carbonum. Plant Cell. 1995;7(11):1941-50. Epub 1995/11/01. doi: 10.1105/tpc.7.11.19417/11/1941 [pii]. PubMed PMID: 8535144.

[92] Itazaki H, Nagashima K, Sugita K, Yoshida H, Kawamura Y, Yasuda Y, et al. Isolation and structural elucidation of new cyclotetrapeptides, trapoxins A and B, having detransformation activities as antitumor agents. J Antibiot (Tokyo). 1990;43(12):1524-32. Epub 1990/12/01. PubMed PMID: 2276972.

[93] Closse A, Huguenin R. [Isolation and structural clarification of chlamydocin]. Helv Chim Acta. 1974;57(3):533-45. Epub 1974/04/27. doi: 10.1002/hlca.19740570306. PubMed PMID: 4857466.

[94] Whitehead L, Dobler MR, Radetich B, Zhu Y, Atadja PW, Claiborne T, et al. Human HDAC isoform selectivity achieved via exploitation of the acetate release channel with structurally unique small molecule inhibitors. Bioorg Med Chem. 2011;19(15):4626-34. Epub 2011/07/05. doi: S0968-0896(11)00458-5 [pii] 10.1016/j.bmc.2011.06.030. PubMed PMID: 21723733.

[95] Wahhab A, Smil D, Ajamian A, Allan M, Chantigny Y, Therrien E, et al. Sulfamides as novel histone deacetylase inhibitors. Bioorg Med Chem Lett. 2009;19(2):336-40. Epub 2008/12/17. doi: S0960-894X(08)01465-0 [pii] 10.1016/j.bmcl.2008.11.081. PubMed PMID: 19084395.

[96] Lobera M, Madauss KP, Pohlhaus DT, Wright QG, Trocha M, Schmidt DR, et al. Selective class IIa histone deacetylase inhibition via a nonchelating zinc-binding group. Nat Chem Biol. 2013;9(5):319-25. Epub 2013/03/26. doi: nchembio.1223 [pii] 10.1038/nchembio.1223. PubMed PMID: 23524983.

[97] Ononye SN, VanHeyst MD, Oblak EZ, Zhou W, Ammar M, Anderson AC, et al. Tropolones as lead-like natural products: the development of potent and selective histone deacetylase inhibitors. ACS Med Chem Lett. 2013;4(8):757-61. Epub 2014/06/06. doi: 10.1021/ml400158k. PubMed PMID: 24900743.

[98] Kapustin GV, Fejer G, Gronlund JL, McCafferty DG, Seto E, Etzkorn FA. Phosphorus-based SAHA analogues as histone deacetylase inhibitors. Org Lett. 2003;5(17):3053-6. Epub 2003/08/15. doi: 10.1021/ol035056n. PubMed PMID: 12916979.

[99] Hui LX. Molecular Design, Synthesis and Simulation of Histone Deacetylase Inhibitors Graduate School of Life Science and Systems Engineering: Kyushu Institute of Technology, Japan 2010.

[100] Wang Y, Stowe RL, Pinello CE, Tian G, Madoux F, Li D, et al. Identification of histone deacetylase inhibitors with benzoylhydrazide scaffold that selectively inhibit class I histone deacetylases. Chemistry & biology. 2015;22(2):273-84. doi: https://doi.org/10.1016/j.chembiol.2014.12.015.