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HISTONE DEACETYLASE: NOVEL TARGET FOR THE TREATMENT OF CANCER

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Abstract

Histone deacetylase inhibitors (HDACI) are the new class of compounds which interfere with the function of histone deacetylase and thereby can release dysregulation of genes that are involved in cell cycle progression, differentiation and/or apoptosis of many tumors. Therefore, several HDACI have exhibited potent antitumor activity in human xenograft models suggesting their usefulness as novel cancer therapeutic agents. These agents also have a long history in the use of psychiatry and neurology as mood stabilizers and anti-epileptics. These are investigated as possible treatment for neurodegenerative diseases (huntington's disease). HDAC inhibitors may represent a new class of compounds for the treatment of RA by simultaneously, coordinately, synergistically, or epigenetically modulating multiple molecular targets in the pathogenesis of RA.

Keywords: HDACI, Histone deacetylase, histone deacetylase inhibitors.

Cancer and Epigenetics

Cancer is characterized by uncontrolled cell division leading to the growth of abnormal tissues¹. When the cells continue multiplying, even though when body needs them, then the result is a mass or growth, called as tumor. Malignant tumors, however often invade near by tissues and organs, spreading the disease. It is possible for cancerous cells, which can freely break from the tumor site and enters into the blood-stream, spreading the disease to other organs. This process of spreading is called as 'metastasis'².

Cancer is considered as an epigenetic disease as it is a genetic and cytogenetic disease³. The genetic effects such as gene mutations and deletions, as well as chromosomal abnormalities, that results in tumor suppressor genes and/or gain of function or hyperactivation of oncogenes⁴. 'Epigenetics' is a term used to describe heritable states of gene expression that are not due to changes in DNA sequence. Epigenetic phenomena have been shown to play an important role in carcinogenesis and tumor progression. Such phenomena also represent potential therapeutic targets for cancer treatment as they are potentially reversible. Two such phenomena⁵ are: Epigenetic changes in DNA methylation and resulting in altered genetic expression and Histone modifications.

Transcriptional silencing of genes via epigenetic mechanisms, such as DNA methylation and post-translational modifications of the histones, is a hallmark of cancer cells. Gene silencing by epigenetic mechanisms is now firmly established as an important contributor to tumorigenesis. Multiple cellular targets, such as tumor suppressors, cell cycle regulators, differentiation regulators and DNA repair genes are silenced by epigenetic mechanisms. Repression of genes epigenetically inactivated can result in the suppression of tumor growth or sensitization to other anticancer therapies. However, this article focuses on histone modifications and the balance of acetylation/deacetylation in tumor cells as a therapeutic target for anticancer therapies⁶.

INTRODUCTION TO HISTONE ACETYLASES AND DEACETYLASES:

Histones are basic proteins around which a strand of DNA is wound and packed into the nucleus and forms nucleosome⁷. The histones are heterogeneous groups and consist of several entities named H1, H2A, H2B, H3 and H4. H1 histones are somewhat loosely bound to chromatin and can be removed by salt solutions. The rest of the chromatin now becomes soluble. When the proteins are freed from chromatin, they tend to associate themselves in a distinct pattern. H3 and H4 aggregate in pairs to form a tetramer (H3₂-H4₂) and H2A and H2B to form dimers (H2A-H2B). Thus H1, H3₂-H4₂ and H2A-H2B form three distinct groupings. The nucleosome core particle which is the fundamental block of chromatin, which is composed of 146-147 base pairs of DNA wrapped around a histone octamer containing one H3-H4 tetramer and two H2A-H2B dimers⁸. The densely packed inactive chromatin is called 'heterochromatin' and the lightly packed active chromatin is called 'euchromatin'. DNA is woven together with

proteins into an intricate organization of both extended euchromatin and condensed heterochromatin. Hyperacetylation is associated with euchromatin which has a more open conformation allowing for increased gene expression, where as hypoacetylation is found in condensed heterochromatin and is coupled with repression of transcriptional activity⁹.

However, histone proteins are the sites of many different types of post-translational modifications which includes the phosphorylation, acetylation, methylation, ubiquitination, sumoylation, and ADP-ribosylation of the eight histones which are mediated by chemical modification of various sites on N-terminal tail. The structural modification of histones is regulated mainly by acetylation/deacetylation of the N-terminal tail and is crucial in modulating gene expression, because it affects the interaction of DNA with transcription-regulatory non-nucleosomal protein complexes. The balance between the acetylated/deacetylated states of histones is mediated by two different sets of enzymes, Histone acetyltransferase (HATs) and Histone deacetylases (HDACs)¹⁰. **Histone acetyltransferases (HATs)** it is known that histone acetyltransferases transfer the acetyl group from acetyl-CoA forming ϵ -N-acetyl lysine on conserved lysines of the N-terminal tails of histones H3 and H4 (and to a lesser extent H2A and H2B). Therefore, **Histone deacetylases (HDAC)** are a class of enzymes that remove acetyl groups from an ϵ -N-acetyl lysine amino acid on a histone¹¹ (FIG. 1).

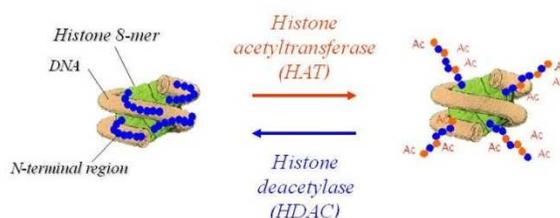


FIG. 1

ACTION OF HISTONE DEACETYLASES:

This includes a study of HDAC expression patterns by which it includes the study of various cancer cell lines as well as a broad selection of primary human tissue samples representing lung, breast, ovary, esophageal,

gastric, colon, thyroid, prostate and pancreatic cancers. Overall, HDAC expression was found to be similar between non-malignant and malignant tissue samples¹².

Aberrant histone deacetylation contributes to tumorigenesis through the recruitment of HDACs to the promoter regions of tumor suppressor genes (TSGs). They also contribute through chromosomal translocations, occurring in certain tumor types, which give rise to oncogenic fusion proteins resulting in inappropriate recruitment of HDACs to certain gene promoters involved in differentiation. CDKN1A, which encodes the cyclin-dependent kinase inhibitor p21^{WAF1/CIP1} that inhibits the cyclin E-CDK2 and cyclin A-CDK2 complexes, is frequently silenced in human tumors. CDKN1A regulates cell cycle progression through the G1/S transition and cellular differentiation. It was found that CDKN1A is transcriptionally inactivated through recruitment of HDAC-containing repressor complexes to an Sp1 binding site in its promoter. Similarly, the CpG island of CDKN2A, which encodes p16^{INK4A}, is hypermethylated and the gene silenced by recruitment of multi-protein complexes containing methyl-CpG binding proteins and HDACs to its promoter¹³

HDAC	DEREGULATION IN CANCER	TUMOR
CLASS I		
HDAC1	Overexpression/underexpression	Esophageal, colon, prostate, CTCL
HDAC2	Overexpression/ mutation	Prostate, colon, gastric, endometrial, CTCL
HDAC3	Overexpression	Prostate, colon
HDAC8	Overexpression	Colon
CLASS IIa		

HDAC4	Overexpression/underexpression/ mutation	Prostate, colon, breast
HDAC5	Underexpression	Colon, AML
HDAC7	Overexpression	Colon
HDAC9	Overexpression/underexpression	Medulloblastomas, astrocytomas
CLASS IIb		
HDAC6	Overexpression	Breast, AML, CTCL
HDAC10	Overexpression	Hepatocellular Carcinoma
CLASS IV		
HDAC11	Overexpression	Breast

TABLE-1

CLASSIFICATION OF HISTONE DEACETYLASES:

In mammals, there are currently 18 identified and have been divided into 4 classes based on cellular localization and function (depending on the homology of transcriptional control factor in yeast).

CLASS I: present in nucleus.

CLASS IIa: present in both nucleus and cytoplasm.

CLASS IIb: It includes only HDAC6 and HDAC10 which are present predominantly in cytoplasm.

CLASS III: SIRT1, SIRT6, SIRT7 present in nucleus; SIRT3, SIRT4, SIRT5 present in mitochondria and SIRT2 in cytoplasm.

CLASS IV: It is being part of both class I and class II enzymes which is present in nucleus and cytoplasm¹⁴.

CLASS	HDAC	HOMOLOGY WITH YEAST	MOL. Wt.
I	1,2,3,8	RPD3 deacetylase	22-25KD
IIa	4,5,7,9	HDA1 deacetylase	20-135KD
IIb	6,10	HDA1 deacetylase	20-135KD
III	SIRT1~7	NAD ⁺ - DEPENDENT SIRT ₂ family	40-50KD
IV	11	Both RPD3/HDA1	39.1KD

TABLE-2

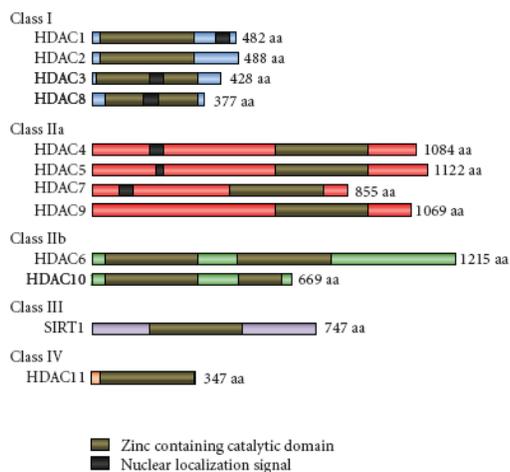


FIG. 2

FIG. 2: The histone deacetylase, family. Schematic representations of class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 6, 7, 9, and 10), class III (SIRT1), and class IV (HDAC11). Structure and Length of HDACs are shown. The total number of amino acid residues (aa) is depicted on the right, next to each HDAC.

FUNCTION OF HISTONE DEACETYLASE:

Histone tails are normally positively charged due to amine groups present on their lysine and arginine amino acids. These positive charges help the histone tails to interact with and bind to the negatively charged phosphate groups on the DNA backbone. Acetylation, which occurs normally in a cell, neutralizes the positive charges on the histone by changing amines into amides and decreases the ability of the histones to bind to DNA. This decreased binding allows chromatin expansion, permitting genetic transcription to take place. Histone deacetylases remove those acetyl groups, increasing the positive charge of histone tails and encouraging high-affinity binding between the histones and DNA backbone. The increased DNA binding condenses DNA structure, preventing transcription¹⁵.

HISTONE DEACETYLASE INHIBITORS:

Histone deacetylase inhibitors (HDAC inhibitors, HDI) are a class of compounds that interfere with the function of histone deacetylase. Inhibition of these HDAC function can release dysregulation of genes involved in cell cycle progression, differentiation and/or apoptosis of many tumors¹⁶. HDAC inhibitors have been shown to alter the activity of many transcription factors, including ACTR, cMrb, E2F1, FEN1, GATA, HNF-4, HSP 90, KU70, NFkB, PCNA, P⁵³, RB, RUNX, SF1SP³, STAT, TFIIE, TCF, YY1. HDAC inhibitors also deacetylate non-histone proteins involved in transcription (p53, p73, E2F1, c-Jun, GATA1, RelA, YY1, Mad/Max, TFIIE, TFIIF, TAT, NF-Y, HMGI, and NF-κB), hormone response (AR and ER), nuclear transport (importin-α7), cytoskeletal structure (α-tubulin), DNA repair (Ku70), DNA structure (the helicase WRN), signal transduction (β-catenin), and the heat shock/chaperone response (HSP90). Hence, HDACI can alter the degree of acetylation of these molecules and therefore increase or repress their activity. Therefore, several HDACI have exhibited potent anti-tumor activity in human xenograft models suggesting their usefulness as novel cancer therapeutic agents¹⁷.

MOLECULAR MECHANISM OF HISTONE DEACETYLASE INHIBITORS:

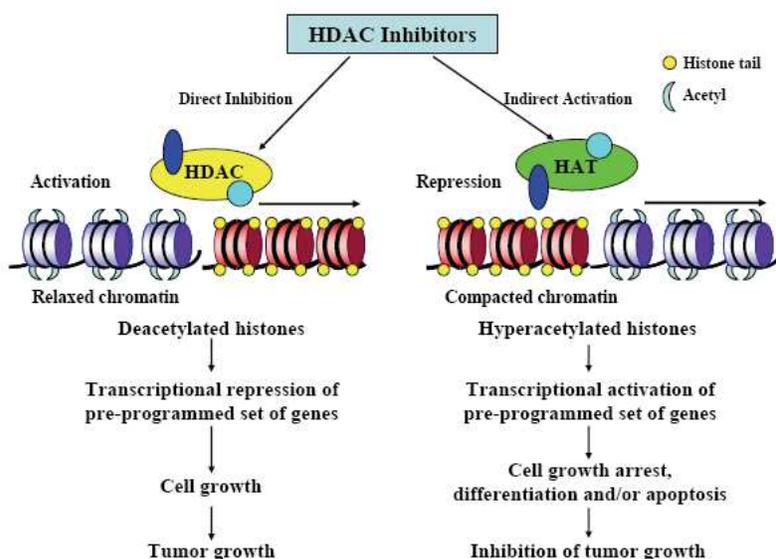


FIG. 3

FIG. 3: Mechanism of HDAC inhibitors in anticancer effects. Transcriptional repression in chromatin with HDAC can lead to cell growth and tumor growth; transcriptional activation in chromatin with HAT can lead to cell growth arrest, differentiation and/or apoptosis and inhibition of tumor growth. HDAC inhibitor can directly inhibit HDAC and indirectly activate HAT.

There are several enzymes, including acetylases and deacetylases, that can regulate transcription by modifying the acetylation state of histones or other promoter-bound transcription factors. These enzymes reveal their involvement in cell-cycle regulation and differentiation. Furthermore accumulating evidence suggests that deregulation of acetylase and deacetylase activity plays a causative role in the generation of cancer¹⁸. Restraining HDAC activity and preventing the deacetylation of histone may induce hyperacetylation of histone, then unfolding ordered chromosome and promote transcription factors combined with DNA, so genes which are inhibited can express and exert the effect of cure tumor (figure 3)¹⁹. HDAC enzymes remove the acetyl group from the histone (hypoacetylation), thereby decrease the space between the nucleosome and the DNA wrapped around it, diminishing transcription factor access and leading to transcriptional repression. The catalytic domain of the HDAC is formed by

a stretch of 390 amino acids containing a set of conserved residues. The active site of the enzyme consists of a curved tubular pocket with a wider bottom. Removal of an acetyl group occurs *via* a charge-relay system, an important component of which is the zinc-binding site at the bottom of the pocket. The presence of a zinc ion at this site is an important factor in the mechanism of action of HDAC inhibitors²⁰.

CLASSIFICATION OF HISTONE DEACETYLASE INHIBITORS:

HDAC Inhibitors are derived from both natural sources and from synthetic routes(TABLE-3). So far these inhibitors more or less, work equally well against class I, class II and class IV HDACs. Compared with agents used initially, some newer agents are effective at even nanomolar concentrations and are relatively less toxic. Several HDAC Inhibitors are currently in phase I/II clinical trials.

Natural and synthetically produced Histone Deacetylase Inhibitors:

GROUP	EXAMPLES
Hydroxamic acid derived compounds	Trichostatin (TSA) Suberoylanilide hydroxamic acid (SAHA) M-carboxycinnamic acid bis-hydroxamide (CBHA) Azelaic bis-hydroxamic acid (ABHA) NVP-LAQ824 Panobinostat Oxamflatin Belinostat Scriptaid Pyroxamide
Cyclic tetrapeptides	Depsipeptide (FK228, FR901228) Apicidin Trapoxin A Chlamydocin Depudesin CHAPS
Short-chain fatty acids	Valproic acid (VA) Phenyl butyrate (PB)

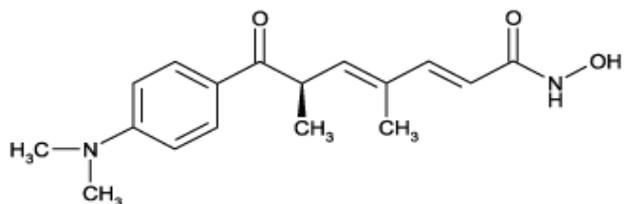
	Phenyl acetate (PA) Sodium butyrate (SB) AN-9 (Pivanex)
Synthetic pyridyl carbamate derivative	Entinostat
Synthetic benzamide derivatives	Tacedinaline
Ketones	Trifluoromethyl ketone α -ketomides

TABLE-3**HYDROXAMIC ACIDS:**

Hydroxamic acids are the most common form of HDACI. The general structure of these compounds consists of a hydrophobic linker that allows the hydroxamic acid moiety to chelate the cation at the base of the HDAC catalytic pocket, while the hydrophobic cap blocks the entrance to the active site. Trichostatin - A (TSA), SAHA, oxamflatin, pyroxamide, and scriptaid, members of this class of inhibitors, potently and reversibly inhibit class I and II HDACs at nanomolar to micromolar concentrations *in vitro*.

Among them, TSA, initially isolated as an anti-fungal antibiotic from *Streptomyces hygroscopicus*, is widely used as a reference HDACI in research. However, its toxicity and low bioavailability have motivated the search for other molecules. The design of many synthetic drugs has been based on the structure of TSA (an aromatic residue cap, hydroxamic acid functional group, and a hydrophobic linker). By using a synthetic program combined with high-throughput screening of compound libraries, newer more potent hydroxamic-based HDACIs such as LAQ824, LBH589 and PXD101 have been successfully identified and are being tested in clinical trials. In particular, LAQ824 inhibits HDAC activity and causes hyperacetylation of the non-histone protein HSP90 thereby inducing proteosomal degradation of Bcr-Abl and ErbB2.

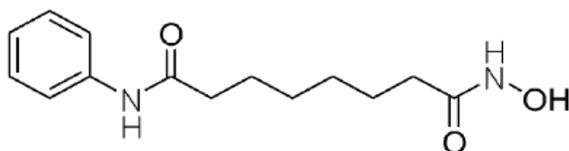
TRICHOSTATIN A:



IUPAC NAMES: (2E, 4E, 6R)-7-(4-dimethylaminophenyl)-N-hydroxy-4, 6-dimethyl-7-oxohepta-2, 4-dienamide²¹.

TSA suppresses the activity of HDAC leading to an increase in histone acetylation. This histone acetylation induces an enhancement of the expression of specific genes that elicit extensive cellular morphologic and metabolic changes, such as growth arrest, differentiation and apoptosis. Trichostatin A has been shown to induce apoptosis in many cancer cells at submicromolar concentrations with very low toxicity toward normal cells²².

SUBEROYLANILIDE HYDROXAMIC ACID (SAHA):

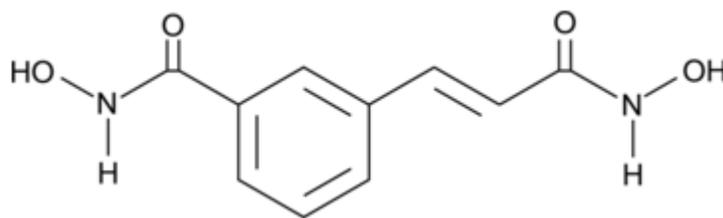


IUPAC NAME: N-hydroxy-N'-phenyloctanediamide

SYNONYMS: N1-hydroxy-N8-phenyl-octanediamide, Zolinza, Vorinostat

SAHA is a histone deacetylase (HDAC) inhibitor that binds directly to the catalytic site of the enzyme thereby blocking substrate access. It inhibits class I and class II HDACs at nanomolar concentrations. SAHA is a drug used to treat a type of cancer called cutaneous T-cell lymphoma, also called CTCL. SAHA is used in patients when the CTCL gets worse, does not go away, or comes back after treatment with other medicines²³.

M-CARBOXYCINNAMIC ACID BIS-HYDROXAMIDE (CBHA):

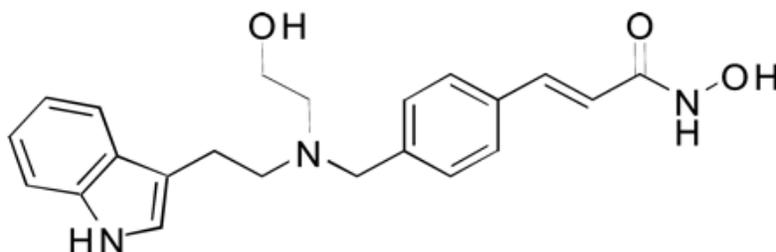


IUPAC NAME: N-hydroxy-3-[(E)-3-(hydroxyamino)-3-oxoprop-1-enyl] benzamide

SYNONYMS: m-Carboxycinnamic acid bis-Hydroxamide; M-carboxycinnamic acid bishydroxamide

CBHA is a member of a recently synthesized family of hybrid polar compounds that have been shown to be inhibitors of HDAC and potent inducers of transformed cell growth arrest and terminal differentiation at micromolar (LD50 range, 1–4 μ M) concentrations. This compound inhibits growth of human neuroblastoma xenografts in vivo alone and synergistically with retinoic acid²⁴.

NVP-LAQ824:



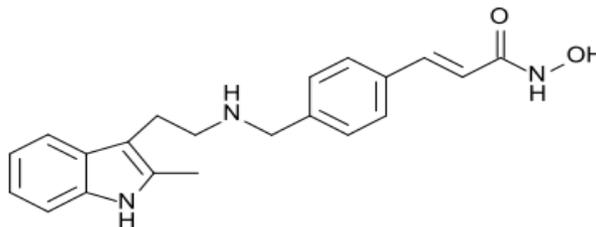
IUPACNAME: ((E)-N-hydroxy-3-[4-[[2-hydroxyethyl-[2-(1H-indol-3 yl) ethyl] amino] methyl]phenyl] prop-2-enamide

SYNONYMS:- NVP-LAQ824; LAQ 824; Dacinostat

LAQ824 is a very potent histone deacetylase inhibitor that is completing phase I clinical trial in solid and hematologic malignancies. LAQ824 has shown impressive antileukemic activity when administered in the low nanomolar range, making it a particularly attractive candidate for clinical development. NVP-LAQ824 is approximately 50000-fold more potent than the HDACI butyrate and its derivatives. It inhibits multiple myeloma cell growth and prolongs survival in a murine myeloma model, without toxicity to normal marrow or peripheral

blood. A phase 1 clinical trial of NVP-LAQ824 in hematologic malignancies is now ongoing at the Dana-Farber Cancer Institute²⁵.

PANOBINOSTAT:

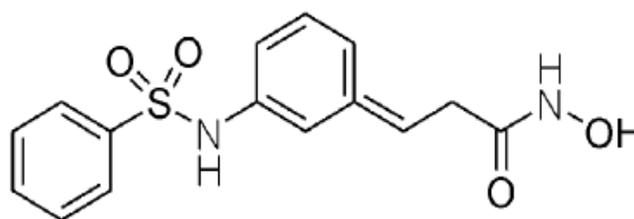


IUPACName: (E)-N-hydroxy-3-[4-[[2-(2-methyl-1H-indol-3yl)ethylamino]methyl]phenyl]prop-2-enamide

Synonyms: LBH-589; LBN-589; LBH589; NVP-LBH589

LBH-589 is a hydroxamic acid based HDACI with a structure similar to vorinostat. It is in phase I clinical trials for cutaneous T-cell lymphoma as an oral agent. It has a longer half-life than vorinostat. In vitro LBH589 induces cell cycle arrest and apoptosis through both caspase dependent and caspase independent pathways in various tumor cell types at nanomolar concentrations. In vivo LBH-589 inhibits tumor angiogenesis as evidenced by blocking new blood vessel formation in human prostate carcinoma cell PC 3 xenografts²⁶.

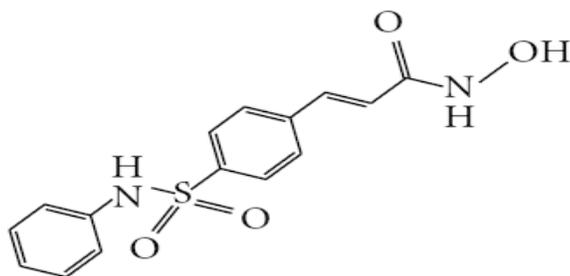
OXAMFLATIN:



IUPAC NAME: (E)-5-[3-(benzenesulfonylamino) phenyl]-N-hydroxypent-2-en-4-ynamide²⁷

SYNONYMS: (2E)-5-[3-(Phenylsulfonylamino) phenyl]-pent-2-en-4-ynohydroxamic acid

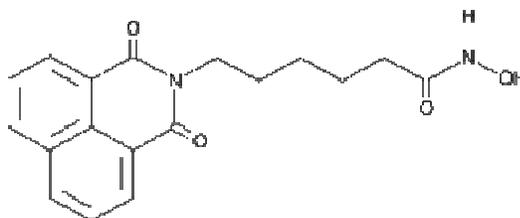
Oxamflatin is a potent inhibitor of histone deacetylases. It has been shown to alter the expression of several genes whose products are involved in cell morphology, motility, apoptosis, and cell cycle control, reducing the proliferation of cancer cells²⁸.

BELINOSTAT:

IUPAC NAME: (2E)-3-[3-(anilinosulfonyl) phenyl]-N-hydroxyacrylamide

SYNONYMS: PXD101; PX105684

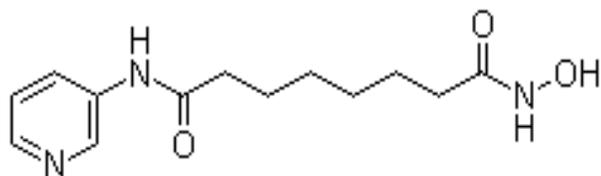
PXD101 was found to inhibit *in vitro* cancer cell growth at sub- to low micromolar IC₅₀ potency, exhibited synergistic activity when used in combination with relevant chemotherapeutics, and effectively inhibited the growth of multidrug-resistant cells. Belinostat is currently under phase I/II testing in lymphoma, ovarian cancer and other solid tumors. It is a potent hydroxamate-type inhibitor of histone deacetylase activity that is cytotoxic *in vitro*, which enhances the effect of cytotoxic chemotherapy, and delays growth in xenograft models of ovarian and colon cancer²⁹.

SCRIPTAID:

IUPAC NAME: N-hydroxy-1,3-dioxo-1H-benz[de]isoquinoline-2(3H)-hexanamide

SYNONYMS: GCK 1026

Scriptaid is a histone deacetylase inhibitor that has an optimal concentration of 6-8 μM in a cell-based assay, is less toxic than trichostatin A, and works in a wide variety of biological systems. It induces cell cycle arrest in colon cancer cells in culture and inhibits tumor growth *in vitro* and *in vivo*. Scriptaid also facilitates the cloning of inbred mouse strains produced by somatic cell nuclear transfer³⁰.

PYROXAMIDE:

IUPAC Name: N'-hydroxy-N-pyridin-3-yl-octanediamide

A synthetic derivative of hydroxamic acid with antineoplastic properties, Pyroxamide inhibits histone deacetylases involved in transcription; induces hyperacetylation of core histones, modulating chromatin structure and affecting transcription of some genes that inhibit tumor growth; and induces growth arrest and apoptosis. Pyroxamide is used in clinical studies for cancer chemotherapy³¹.

CYCLIC TETRA PEPTIDES:

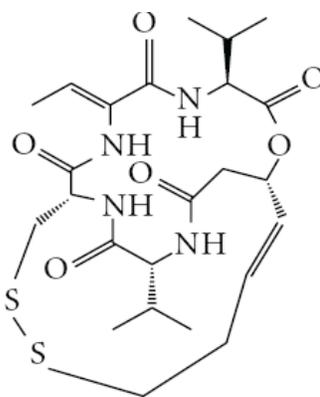
Cyclic peptides having epoxyketone (epoxides) may act by chemically modifying an active site nucleophile with the epoxy group and forming H-bonds with ketone. These chemicals are supposed to trap HDACs through the reaction of the epoxide moiety with the zinc cation or an amino acid (forming a covalent attachment) in the binding pocket. However, the lability of the epoxide functionality prevents significant *in vivo* activity, which makes them of little pharmacologic interest. The only HDAC inhibitors in this set of compounds are a number of natural products with significant *in vitro* activity, such as trapoxin (TPX) A and B, depudecin, and 2-amino-8-oxo-9, 10-epoxydecanoic acid. TPX is a hybrid molecule containing cyclic peptide (acts as hydrophobic cap) and epoxyketone moiety that has shown irreversible inhibition of mammalian HDACs at nanomolar ranges.

Cyclic tetrapeptides such as apicidin, which has an ethyl ketone moiety, and FK228 (FR901228, also referred to as depsipeptide) inhibit HDACs at nanomolar concentrations. Apicidin is a fungal metabolite that is able to inhibit HDACs and proliferation of tumor cells via induction of p21*WAF1/Cip1* and gelsolin. It is postulated that apicidin interacts with the catalytic site and has been shown to inhibit cell proliferation in several human cancer cell lines

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because of its anti-invasive and antiangiogenic activity. FK228 is a natural product derived from *Chromobacterium violaceum* that exhibits potent antitumor activity through currently unknown mechanism of action.

One hypothesis proposes that the disulfide bridge is reduced inside the cell or organism and the 4-mercaptobut-1-enyl residue then fits inside the HDAC catalytic pocket, chelating Zn²⁺ in a manner similar to that of other inhibitors. In cultured cells, it is able to induce histone hyperacetylation and growth arrest at nanomolar concentrations. In human leukemia cells, FK228 had an IC₅₀ at nanomolar concentrations and induced apoptosis in cells from patients with chronic lymphocytic leukemia. In addition, depsipeptide has been shown to be antiangiogenic by modulating expression of c-myc and other regulatory genes. FK228 is currently undergoing extensive evaluation in clinical trials³².

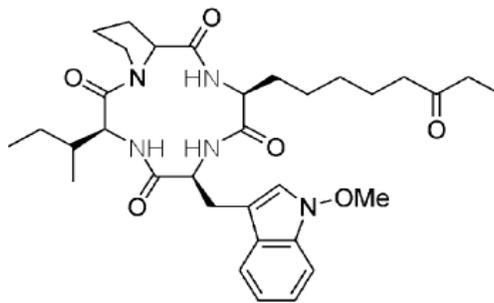
DEPSIPEPTIDE:



SYNONYMS: Romidepsin, Istodax, FK 228, FR901228

Romidepsin acts as a histone deacetylase inhibitor, loosening DNA which may allow some genes to be turned on and others turned off. This interaction ultimately leads to apoptosis (death of the cancer cells). Romidepsin is a novel anti-cancer agent being studied for the treatment of T-cell non-Hodgkin's lymphoma. Specifically it is in stage II trials for cutaneous T-cell lymphomas (CTCL) such as Mycosi fungosides and Sezary syndrome and studies are planned for peripheral t-cell lymphoma (PTCL) and possibly other types of cancer.

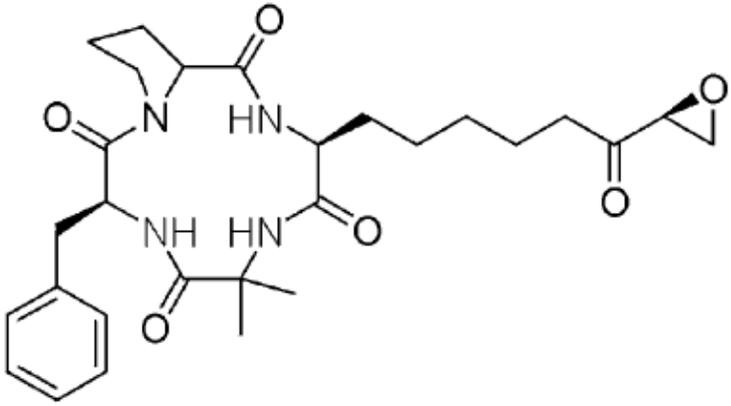
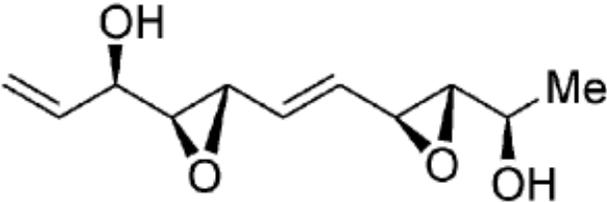
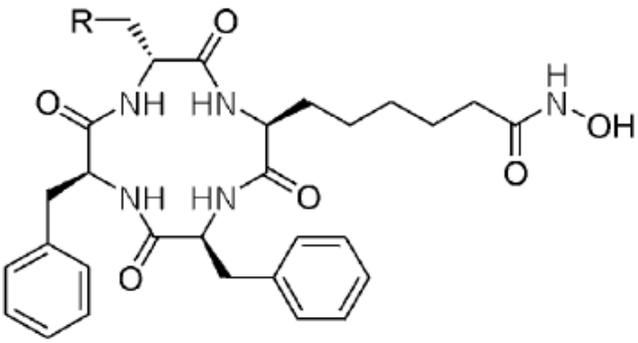
APICIDIN:



IUPAC NAME: Cyclo (N-O-methyl-L-tryptophanyl-1-isoleucinyl-d-pipecolinyl-L-2-amino-8-oxodecanoyl))

Potent inhibitor of histone deacetylase. Inhibits proliferation. Induces cell cycle arrest at the G1 phase. At 100nM it induces a long lasting hyperacetylation of histone H4 while that induced by trichostatin is transient. Stimulates apoptosis. Apoptosis is induced via induction of Fas/Fas ligand. Displays potent antiangiogenic effects and dramatically decreases HIF-1 α protein levels and transcriptional activity in human and mouse tumor cell lines. Antiprptzoal.

OTHER DRUGS OF CYCLIC PEPTIDES	STRUCTURES
<p>HC-TOXIN</p> <p>[Cyclo-(D-Pro-L-Ala-L-2-amino-8-oxo-9,10-epoxydecanoic acid)]</p>	

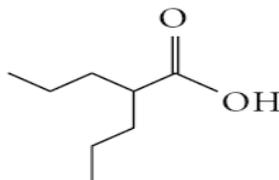
<p>CHLAMYDOCIN</p> <p>[Cyclo(phenyl alanyl propyl-2-amino-8-oxo-9,10-epoxy decanylalanyl)]</p>	
<p>DEPUDESIN</p> <p>(2R,3S,4S,5E,7S,8S,9R)-2,9- dihydroxy-3,4;7,8-diepoxy-undeca-5,10 diene</p>	
<p>CHAPS</p> <p>3-[(3-Cholamidopropyl) dimethylammonio]-1 propanesulfonate</p>	

SHORT-CHAIN FATTY ACIDS:

Butanoic acids, valproic acids (VPA), and 4-phenylbutanoic acids all belong to this group of HDACIs. Short-chain fatty acids have low potency because of their short side chains, limiting contact with the catalytic pocket of HDACs. VPA, used clinically as an anti-convulsant, inhibits HDAC activity *in vitro* at millimolar concentrations and has much weaker binding affinity. VPA selectively induced the degradation of HDAC2 *in vitro* and *in vivo*. Phenyl acetate (PA), a well studied member of the short-chain fatty acids, is a metabolite of phenyl butyrate (PB)

that arrests cells in G1 by inducing the expression of p21. PA can penetrate the central nervous system and when tested in solid tumors showed anti-tumor effects mediated by histone acetylation³³.

VALPROIC ACID:-

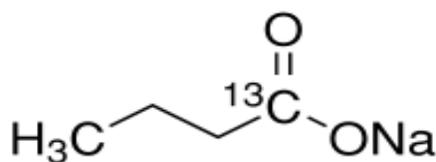


IUPAC NAME: 2-propylpentanoic acid

SYNONYMS: Dipropylacetic acid, VPA, myproic acid

Valproic acid (VPA) has been used in the treatment of epilepsy for almost 30 years. The compound has recently been shown to have activity as HDAC inhibitor. Valproic acid inhibits both class I and II HDACs, with a high potency for class I HDACs. Valproic acid inhibits HDAC activity in vitro, most likely by binding to the catalytic center of HDACs. More importantly, valproic acid induces differentiation of carcinoma cells, transformed hematopoietic progenitor cells and leukemic blasts from acute myeloid leukemia patients³⁴.

SODIUM BUTYRATE:



IUPACNAME: Sodium Butanoate

SYNONYMS: NaB, SB, NaBu, Butanoic acid sodium salt, Sodium propanecarboxylate

Sodium butyrate is able to induce cell cycle arrest, differentiation and apoptosis in various cancer cells. The compound in millimolar concentrations causes an accumulation of acetylated histone species in a variety of

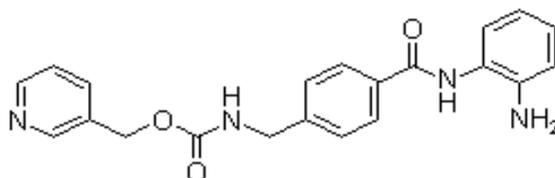
vertebrate cell lines. Sodium butyrate, a short-chain fatty acid, is the most common and physiologic member of HDAC inhibitors because it is formed in the colon by fermentation of dietary fibers³⁵.

BENZAMIDES:

The synthetic benzamide derivatives include a structurally diverse group of compounds such as MS-275 and CI-994. CI-994 has shown efficacy in solid tumors in murine models but did not inhibit HDAC directly. The mechanism of its action is unknown, but it seems to inhibit both histone deacetylation and cellular proliferation at the G1-S phase transition. MS-275 and some of its derivatives inhibit HDACs in vitro at micromolar concentrations, but the mechanism is not clearly understood. It is believed that the diaminophenyl group is very important for the inhibitory behavior; probably, both amino functionalities chelate the metallic ion in the catalytic site.

MS-275-associated HDAC inhibitory activity is accompanied by an increase in expression of cyclin-dependent kinase inhibitor p21 *WAF1/Cip1* and accumulation in G1 phase. MS-275 displays antiproliferative activity in several human cancer cell lines, including breast, colorectum, leukemia, lung, ovary, and pancreas. MS-275 suppressed growth of several pediatric cancer cell lines in a dose-dependent manner, as well as tumors transplanted in nude mice. MS-275 and CI-994 are undergoing clinical trials. There are reports of novel nonhydroxamate sulfonamide anilides similar in structure to MS-275 being synthesized that have shown lower toxicity and comparable antiproliferative activity. Focus is on the development of novel compounds based on core structures of HA or benzamide platform, which may have a better HDAC inhibitory profile and lower toxicity compared with parent compounds³⁶.

ENTINOSTAT:



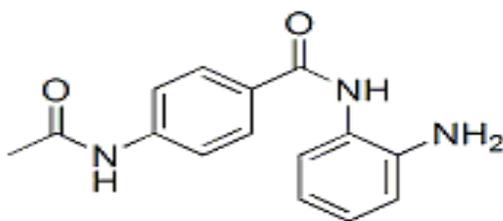
IUPAC NAME: pyridin-3-ylmethyl 4-(2 amino phenyl carbamoyl) benzyl carbamate

SYNONYMS: SNDX-275; MS-27-275

Entinostat preferentially inhibits HDAC 1 compared with HDAC 3 and has little or no effect against HDACs 6 and 8. The amine group of the benzanilide moiety might act as a hydrogen bond donor or could be involved in other electrostatic interactions, which are necessary for inhibitory activity.

Currently, MS-275 (in combination with azacitidine) is in a clinical phase I/II trials for myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia with multilineage dysplasia. This compound (in combination with azacitidine) is also in clinical phase I/II trials for patients with recurrent advanced nonsmall-cell lung cancer³⁷.

TACEDINALINE:



IUPAC NAME: 4-(acetylamino)-N-(2-aminophenyl) benzamide

SYNONYMS: PD-123654, GOE-5549, Acetyldinaline, CI-994

Tacedinaline is a novel orally active compound with a wide spectrum of antitumor activity in preclinical models, in vitro and in vivo. The mechanism of action of CI-994 is not entirely understood but it has been shown to inhibit HDAC-1 and HDAC-2 and cellular proliferation. CI-994 originally was developed as an anticonvulsant agent and later was reported to have antitumor activity. Entinostat preferentially inhibits HDAC 1 compared with HDAC 3 and has little or no effect against HDACs 6 and 8. The amine group of the benzanilide moiety might act as a hydrogen bond donor or could be involved in other electrostatic interactions, which are necessary for inhibitory activity³⁸

U.S. FDA APPROVED DRUGS:

Vorinostat and Romidepsin are the two HDAC inhibitors approved by U.S.FDA³⁹. These drugs are approved for cutaneous T-cell lymphoma (CTCL) Phase I/II in hematological malignancies and solid tumors⁴⁰.

Conclusion

HDACIs represent novel anti-cancer drugs which not only regulate transcription, but also induce various cellular effects including growth arrest, differentiation, and apoptosis and these effects are specific to cancer cells. Over the past decade a better understanding of epigenetic mechanisms that attribute to tumorigenesis has created a great opportunity for the clinical development of novel epigenetic targeted therapies. HDAC inhibitors are promising therapeutic agents, even though their exact targets and mechanisms of cancers has encouraged further development of HDAC inhibitors. Combination therapy with other medicines will yield improved clinical outcomes over those seen with single agent in the treatment of cancer patients. Through these coordinated approaches in basic, translational, and clinical fields, the use of HDACIs is expected to open up a new era in mechanism-based cancer therapy.

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