Original Research Paper Chemistry

Review on Histone Deacetylase Inhibitors: Mechanism of Action and Therapeutic Uses in Cancer

Kruti D. Maniya Shree Dhanvantary Pharmacy College, Department of pharmaceutical chemistry

Malleshappa N. Noolvi Shree Dhanvantary Pharmacy College, Department of pharmaceutical chemistry

ABSTRACT

Histone deacetylases (HDACs) are the class of enzymes that remove the acetyl groups of ε-N-lysine amino acid residues of histone tails leading to chromatin compaction and transcriptional repression. HDACs can also influence transcription-independent such as mitosis or deoxyribonucleic acid (DNA) repair and deacetylate non histone proteins involved in cell proliferation and death, altering their function. Histone deacetylase inhibitors (HDACi) interfere the function of the HDACs. HDACi have been shown to induce differentiation, cell-cycle arrest, and apoptosis and to inhibit migration, invasion, and angiogenesis in many cancer cell lines. These compounds inhibit tumor growth in animal models and show antitumor activity in patients. HDACi alone and in combination with a variety of anticancer drugs are being tested in clinical trials, showing significant anticancer activity both in hematological and solid tumors. SAHA (vorinostat, Zolinza) was the first HDACi approved by the US FDA.

KEYWORDS : Histone deacetylase inhibitors, Anticancer, Treatment.

Histone Deacetylase (HDAC)

HDACs have emerged as crucial transcriptional co-repressors in highly diverse physiological and pathological systems. Histone Deacetylases are the class of enzymes that remove acetyl group form ε-N-Acetyl lysine aminoacid on histone & it allows the histone to wrap DNA more tightly. DNA expression is regulated by histone acetylation and methylation. It being involved in RNA synthesis and being highly associated with nuclear chromatin.

Histone Acetylation determine by the enzymatic activities of both Histone acetyltransferases (HATs) and Histone deacetylases (HDACs).

Classification of HDACs

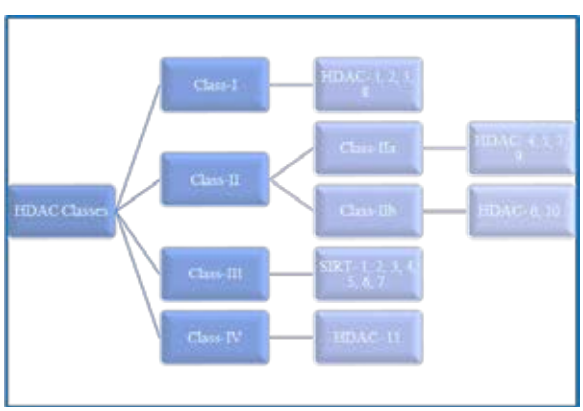


Fig.1 Classification of HDAC

There are four main class of histone deactylase based on the cellular localization and function. Class I, II, IV considered as classical whose activity are inhibited by trichostin A and Zinc dependent active site. Where, class III considered as sirtuins and NAD^+ dependent protein.

Class I includes HDACs1, 2, 3 and 8 that are primarily nuclear. Class II are primarily localized to the Cytoplasm, these class divided into class IIa and class IIb. Class IIa includes HDACs 4, 5, 7 and 9 and class IIb includes 6 and 10 which contain two catalytic site. Class III includes SIRTs 1, 2, 3, 4, 5, 6, 7 and Class IV include HDACs 11.

A typical characteristic of human cancer is the deregulation of DNA methylation and posttranslational histone modifications in particular histone acetylation which has the fatal consequences of gene transcription deregulation.

The role of HDACs in cancer is not restrictef to their contribution to histone deacetylation but also to their role in deacetylation of non-histone protein. For example, HDAC1 interacts with the tumor suppressor p53 and deacetylate it. *in vivo* and *in vitro* p53 is phosphorylated and acetylated under stress conditions. Since lysine residues acetylatd in p53 overlap with those that are ubiquitinated. P53 acylation serves to promote protein stability and activation, inducing checkpoints in the cell-division cycle, permanent cell-division arrest and cell death.

HDAC Inhibitors

The association of HDAC enzymes and carcinogesis has increased interest in the use of HDAC inhibitors as antitumor agents. HDAC inhibitors have been shown to induce cell cycle arrest, growth inhibition, chromatin decondensation, differentiation and apoptosis in several cancer cell types.

HDAC inhibitors are classified by structure.

Short chain fatty acids- Butyrate and Valproic acid (VPA)

Hydroxamates- Trichostatin A, SAHA (suberoylanilide hydroxamic acid or Vorinostat), Panobinostat (LBH589), Oxamflatin, Tubacin and Belinostat (PXD 101).

Benzamides- Entinostat (SNDX25), Mocetinostat (MGCD0103).

Cyclic tetrapeptides- Romidepsin (FK228), Trapoxin A, Apicidin.

The compounds are vary in structure as well as they have have also the distinct affinity for the different HDACi. The Short chain fatty acids (Butyrate and Valproic acid) and Trapoxin A are the class I and class IIa HDACi. Entinostat (SNDX275) is more specific that inhibit class I HDACs but not HDAC8. Romidepsin (FK228) inhibit HDAC1 and HDAC2. Tubacin inhibit HDAC6. The HDAC inhibitory activity of the naturally occurring compound Butyrate and Valproic acid which are responsible for the ability to cause the cell cycle arrest and differentiation of the transformed cell. Hydroxamates like Vorinostat (SAHA) was the first new HDACi which approved by the FDA October 2006 for the clinical use in the cancer patient for the treatment of cutaneous T-cell lymphoma. Vorinostat. (SAHA) was evaluated in phase I clinical trials as an i.v. and orally administered drug. Patients included those with hematologic (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma) and solid malignancies (prostate, bladder, breast, colon, ovarian, and renal). In the both trials, there was significant anticancer activity at doses that were well tolerated by patients. More than 50 clinical trials with combination therapy with Vorinostat (SAHA) and various agents (carboplatin, paclitaxel, 5-fluorouracil,

etc.) in patients with advanced hematologic and solid tumors are in progress. Hydroxamates induce the differentiation or apoptosis of the cancer cell line or both. Mainly use in the treatment of cutaneous T-cell lymphoma. Panobinostat (LBH589) is a hydroxamic acid–based HDACi with a structure similar to Vorinostat.

HDAC Mechanism of Action

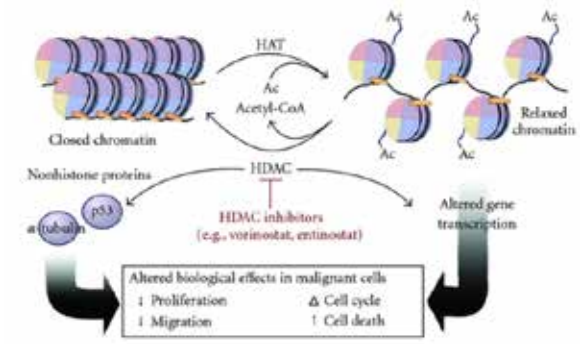
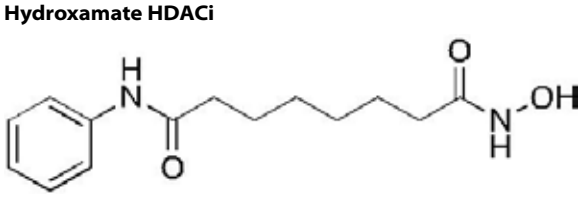


Fig.2 Mechanism of action of HDAC

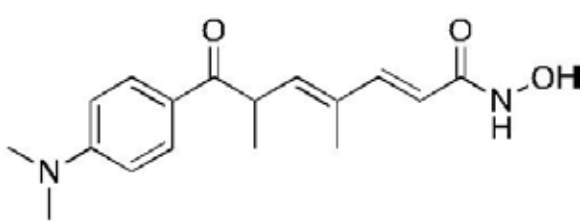
Chemistry of HDACs inhibitors

HDACi can be divided into several structural classes including hydroxamates, cyclic peptides, aliphatic acids, and benzamides TSA was the first natural hydroxamate discovered ti inhibit HDACs. Vorinostat is structurally similar to TSA. A series of aminosuberoyl hydroxamic acids have recently been discovered to inhibit HDACs and transform cell proliferation at nanomolar concentrations. Vorinostat is the first HDACi to be approved for clinical use by the Food and Drug Administration. Vorinostat is a pan-inhibitor of class I and class II HDAC proteins. M-Carboxycinnamic acid bishydroxamate is a potent HDACi and is the structural basis for several derivatives including LAQ-824, LBH-589, and a sulfonamide derivative, belinostat (PXD-101), TopoTarget AS/Cure Gen Coop; ref. These HDACi inhibit class I and class II HDACs. Panobinostat (LBH-589; Novartis AG) is a cinnamic hydroxamic acid analogue of M-carboxycinnamic acid bishydroxamate. IF2357 (Italfarmaco SpA) is an HDACi that contains a hydroxamic acid moiety linked to an aromatic ring. A series of aryloxyalkanoic acid hydroxamides have been synthesized that are HDACi at nanomolar concentrations.

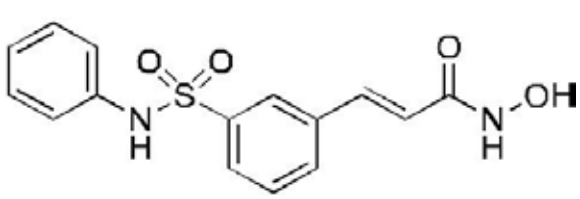
Hydroxamate HDACi



Vorinostat

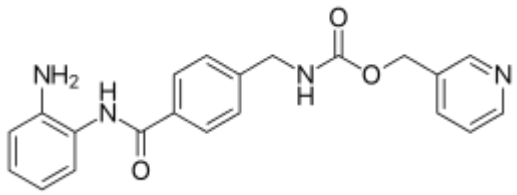


Trichostatin A

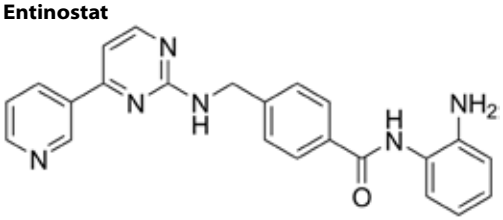


Belinostat

Benzamides HDACi

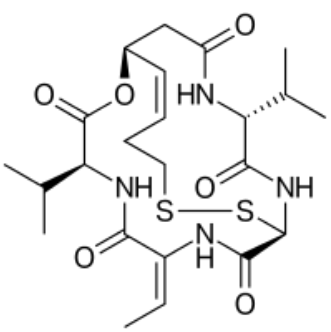


Entinostat

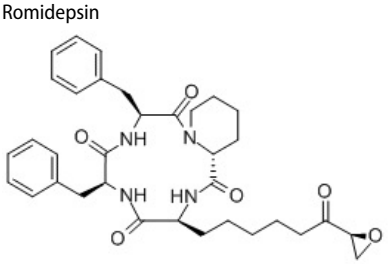


Mocetinostat

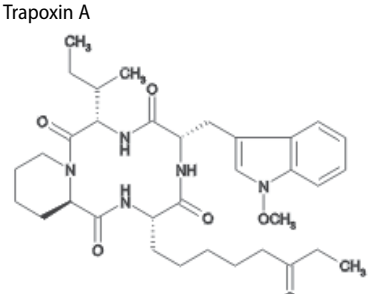
Cyclic Tetrapeptides



Romidepsin



Trapoxin A



Apicidin

HDAC Biological Activity

Class I HDACs are mostly localized within the nucleus where Class II shuttle between nucleus and cytoplasm. Class I play a role cell survival and proliferation, and class II HDAC have HDACs have tissue specific roles. Class III contains the structurally diverse NAD^+ dependent sirtuin family, which does not act primarily in histones. Class IV which is

previously as a part of both Class I and Class II.

Non target HDACs include p53, E2F, GATA-1, YY1, ReIAMaD-Max, c-Myc, NF-kB, HIF-1α, Ku70, α-tubulin, STAT3, Hsp90, TFIIE, TFIIF, and hormone receptors explain some biological activity. HDACs expression and activity can be altered in many cancers and in both lymphoma and leukemia HDACs is associated with the function of oncogenic-translocation products, such as PML-RAR*α* in acute promyelocytic leukemia.

References

1. Zahonero BB and Parra M, "Histone deacetylase and cancer." *Molecular Oncology*, **2012,** *6,* 579-582.
2. Marks PA, "Histone Deacetylase inhibitors: A chemical genetics approach to understanding cellular functions." *Biochimica et Biophysica Acta,* **2010,** *1799,* 717-725.
3. Iglesias OM, Liorente LR, Garcia L, Zambrano A and Aranda A, "Histone deacetylase inhibitors: mechanism of action and therapeutic use in cancer." *Clinical and Translational Oncology,* **2008,** *10,* 395-398.
4. Mars PA, Rifkind RA, Richon VM, Breslow R, Miller T and Kelly WK, "Histone deacetylases and cancer:causes and therapies." *Macmillan Magazines Ltd*, **2001**, *1,* 194-202.
5. Marchion D and Munster P, "Development of histone deacetylase inhibitors for cancer treatments." *Expert Review Anticancer Theory*, **2007,** *7,* 583-593.