# Histone Deacetylase Inhibitors: A Prospective In Drug Discovery

Rakesh Yadav, Pooja Mishra, Divya Yadav

Department Of Pharmacy, Banasthali University, Banasthali, Rajasthan, India

**Abstract**

Treatment of cancer is a major provocation in the entire society and follows a line of an investigation in the field of drug discovery. Therefore, there is a crucial requirement of discovering an ingenious medicinally active agent with proficiency of amending idle drug targets. Increasing pragmatic evidences implies that the histone deacetylases (HDAC) are trapped in cancer progression which increases the deacetylation and triggers malignancy changes. They provide a ground-breaking scaffolds and an attainable key for investigating chemical entity pertinent to HDAC biology as a therapeutic target in drug discovery context. Due to the gene expression, an impending requirement to prudently transfer cyto-toxicity to cancerous cells, HDAC inhibitor may be developed as an anti-cancerous agent. The present review has been focused on the basics of HDAC enzyme, their inhibitors and therapeutic outcomes.

**Keywords:** Histone deacetylase inhibitors, Apoptosis, Multi-therapeutic approach, Cancer

# Histon Deasetilaz İnhibitörleri: İlaç Keşfinde Bir Aday

**Öz**

Rakesh Yadav, Pooja Mishra, Divya Yadav

Eczacılık Fakültesi, Banasthali Üniversitesi, Banasthali, Rajasthan, Hindistan

Kanser tedavisi tüm toplum için büyük bir kışkırtıcıdır ve ilaç keşfi alanında bir araştırma hattını izlemektedir. Bu nedenle, işlemeyen ilaç hedeflerini iyileştirme yeterliliğine sahip, tıbbi aktif bir ajan keşfetmek için hayati bir gereklilik vardır. Artan pragmatik kanıtlar, histon deasetilazların (HDAC) kanserin ilerleme aşamasında deasetilasyonu arttırarak ve malignite değişikliklerini tetikleyerek kapana kısıldığını ifade etmektedir. HDAC inhibitörleri, ilaç keşfi bağlamında terapötik bir hedef olarak HDAC biyolojisiyle ilgili kimyasal varlığı araştırmak için, çığır açıcı iskele ve ulaşılabilir bir anahtar sağlarlar. HDAC inhibitörünün gen ekpresyonu yoluyla, kanserli hücrelere sitotoksisiteyi ihtiyatlı bir şekilde aktarmak için anti-kanser bir madde olarak geliştirilmesi yaklaşan bir gerekliliktir. Bu derlemede HDAC enziminin temelleri, inhibitörleri ve terapötik sonuçları üzerinde durulmuştur.

Anahtar Kelimeler: Histo deasetilaz inhibitörleri, Apopitoz, Çoklu tedavi yaklaşımı, Kanser

## Introduction

In recent years, an immense development has been made in the management of the cancer due to which life expectation of the cancer patients has been improved drastically. Cancer is represented by an inapt cell proliferation or transformation.[1] In cancerous cells, genes undergo various modification processes either by mutation or epigenetics. A number of potential approaches have been proposed for the treatment of cancer, but the histone deacetylases inhibitors (HDACI) is the emerging one.[2] Various reports in the literature revealed that certain HDAC family members are aberrantly expressed in the several tumors and have a non-redundant function in controlling the hallmarks of cancerous cells. They are classified into the two type i.e. Zn-dependent (Class I and Class II) and NAD-dependent (Class III) enzymes. Currently, researchers over the globe are paying more attention in the modification of Zn-dependent portion of the histone family. At present, there are total eleven HDAC family members identified on the basis of their similarity chain (**Fig. 1**).[3-4]

Histone deacetylases (HDACs) are the enzymes that catalysis the deacetylation of lysine remnants located at the *N*-terminal of several protein substrates, such as nucleosomal histones. Histone acetylation is an important key of the gene expression. Histone acetyl transferases and histone deacetylases are the two types of enzymes which are primarily amenable for the catalysis of particular lysine residues of histones.[5] Enzymes inhibitors are well-known to stimulate cell cycle arrest, p53 sovereign, initiation of cyclin dependent kinase inhibitor i.e. p21, tumor discriminating apoptosis, and segregation of normal and malignant cells. Histone deacetylases inhibitors have currently pulled significant interest in the treatment of cancer as well as other human disorders.[6]

Numbers of HDAC inhibitors have been reported till date, which produces tumor cells growth arrest, at doses that are apparently nontoxic and appear to be very selective.[1] The HDAC inhibitors consists of three defined structural parts of ideal pharmacophore i.e. (a) recognition cap group (b) hydrophobic linker and (c) the zinc-binding group (**Fig. 2** [7, 8]). Earlier, HDAC inhibitors highlighted the alteration of the surface recognition site (capping group) and the zinc ion binding group.[5] Some of the selective HDAC inhibitors would help in clarifying the position entity of histone deacetylases protein into cancer and having prospective to be improved therapeutic profile. Additionally to changing the metal binding site, the hydrophobic site is also

varied, concentrating on modifying linker site by varying unsaturation and adding ring (e.g. aryl, cyclohexyl) inside the series, [9] but still selective and potent HDACIs yet to be investigated.

On the basis of chemical structures and enzymatic activities, HDACIs are (**Fig. 3** [10]) chemically classified as i.e., *hydroxamates* (vorinostat, panobinostat, givinostat, quisinostat, abexinostat, belinostat, tefinostat, resminostat, pracinostat), *benzamides* (entinostat, mocetinostat, chidamide), *aliphatic acids* (valproic acid), and *cyclic peptides* (Romidepsin).[11] They all posses to trigger diverse functions like cell-cycle detain, angiogenesis, immune modulation and cell-demises by highlighting non-histone proteins as well as histone protein. [9] Large number of HDAC inhibitors are originated from natural sources which shows substantial effect against cancer cells. Some of the examples of natural HDAC inhibitors are tabulated in **Table 1**. [12-14]

**FDA approved and clinical trial drugs**

Vorinostat, romidepsin, belinostat and romidepsin are three histone deacetylase inhibitors which are consented by the Food and drug administration for the dealing of cutaneous T-cell lymphoma. At present, there are more than eighty clinical trials considering, except 11 diverse histone deacetylase inhibitors for solid and hematological tumors, moreover single and in combination with a variety of other anti-tumor drugs shown in **Table 2**.[3]

**Hydroxamic Acids**

Number of histone deacetylase inhibitors has been identified and some are under clinical trials with hydroxamic acids scaffold for the treatment of various types of cancer. The hydroxamic acid based drug molecule consists three defined structural parts of ideal pharmacophore i.e. (a) recognition cap group (b) hydrophobic Linker and (c) the zinc-binding group. Most of the of histone deacetylase inhibitors the cap side and amino acid are act together in the channel, and a linker of which have four to 6 unit of carbon reason of the subsequent Zn binding group that bind to the Zn ion for enzyme inhibition. [15]

*Trichostatin A (TSA)* is a first hydroxamate based histone deacetylases inhibitor that was isolated from *Streptomyces hygroscopicus* to inhibit HDACs. Merely, R- isomer of Trichostatin A was found to be active against histones deacetylases. [16]

*Vorinostat* (*N*-hydroxy-*N*'-phenyl-octanediamide) is marketed in the name of Zolinza® by Merck, was the one of the first histone deacetylases inhibitor permitted for the treatment of CTCL (cutaneous T-cell lymphoma) in the year 2006 by the FDA [17] Vorinostat hinders all

classes of HDAC proteins (I, II and IV), except Class III HDAC which is a $NAD^+$ dependent. [18-19]

*Panobinostat (LB589)* is a new drug developed by Novartis for the treatment of various cancers [20] and approved by US-FDA in 2015 for the treatment of multiple myeloma. [21-23]

*Givinostat (ITF2357)* has been reported as a hydroxamic acid based HDACi revealed positive effects in patients having Hodgkin's lymphoma, multiple myeloma and severe lymphocytic leukemia. European Union has designated givinostat as an orphan drug for the treatment of systemic juvenile idiopathic arthritis and polycythaemiavera.[24]

*Abexinostat (PCI-24781)* has been reported as a potent hydroxamate based HDACi having a wide range of spectrum on anticancer activities. Either it is used as alone or in hybrid with the proteasome inhibitors in the treatment of neuroblastoma cell lines. [25] Abexinostat used with usual chemotherapy agents, or used for different type of carcinomas e.g. tissue STS (sarcoma models of human). [26]

*Belinostat (Beleodaq* or *PXD101)* is a novel hydroxamate-type HDAC inhibitor that exhibits *in vitro* cytotoxicity at low micromolar concentrations and it is active against spectrum pharmaceutical for the treatment of ovarian cancer, CTCL, thymo or thymic carcinoma myelodysplastic syndrome. This drug showed remarked effect on single or combinational therapy. [27]

*CUDC 101* is multi targeted enzymes and receptors like HDAC, TK (tyrosine kinases), EGFR (epidermal growth factor receptor) and HER2 (human epidermal growth factor receptor-2) and it possess potent anti-proliferative and pro-apoptotic activities. [28]

*Pracinostat (SB939)* is another clinical trial (phase-II) compound with HDAC inhibitory activity. Studies postulated that the activity or acceptability of compound **8** is in transitional / high risk myelofibrosis (MF) affected patients. [29] The drug has also been tested for modified solid tumor [30] with no promising results. The drug also showed better affectivity in children who's having refractory solid tumors. [31]

*Resminostat* abolishes cell growth and robustly persuaded apoptosis in multiple myeloma cell lines in small μm concentration. [32] This drug show significant effect when dispensed in combination with other drug (melphalan, bortezomib). [33] In Phase II clinical trials, it showed positive effect in Hodgkin's Lymphoma and was also evaluated for higher colorectal malignancy. [34]

*Quisinostat (JNJ-26481585)* is an experimental drug discovered by Johnson's and Johnson's through the clinical studies. The data suggests that it is "pan" inhibitor and found to be effective for the treatment of CTCL, leukemia myeloid in nanomolar concentration. [35]

*Tefinostat* or CHR-2845 (cyclopentyl 2- ((4- ($N^1$hydroxyoctanediamido) cyclohexyl) methylamino) -2-phenylacetate) comes under hydroxamic acid category used as particular substrate for hCE-1(intracellular carboxyl-esterase), whose phrase is limited to cells of the family of monocyte/macrophage. It is a monocyte or macrophages focused HDACi which is cleaved to an active acid and possess significant effect towards myeloid leukemia. Phase I clinical trial of the drug showed remarked effect on hematological malignancies and lymphoid tumor. [36]

*CHR-3996* is a next generation histone deacetylases inhibitor based on hydroxamic acid and showed greater potency towards class I HDACi with latent anti-neoplastic effect and also showed potential effect for the modified malignancies in clinical trials. [37, 38]

**Benzamide Derivatives**

This is another class of histone deacetylases inhibitor having 20 amino anilide moiety capable to get in touch with definite amino acids in the active site of histone deacetylases core, either through or lacking of zinc ion chelation. [39]

*Entinostat (MS-275)* was found to potentially inhibit various cancer cells like NSCLC, breast malignancy, lympho-blastic cancer, colon and renal cancer, meta-static tumor etc and also has remarked effect in different phases of clinical trials and with selectivity towards class 1. [40]

*Mocetinostat (MGCD0103)* is an isotype of histone deacetylase inhibitor and showed in vitro activity against HDAC1 selectively and some activity against the various isoforms of HDAC (2, 3 and 11). [41] The drug showed greater potency in hematological leukemia,[42] lymphoma cancer [43] and solid malignancy. [44]

*Chidamide (Epidaza)* is an HDAC inhibitor developed and approved in China (2015) that showed potential effects in treatment of the pancreatic cancer. [45]

**Short Chain Fatty Acid**

The chemical class of short chain fatty acid has been also introduced has HDAC inhibitors. Their mode of action is based on the presence of COOH group which are covering the acetate fleeing channel that have Zn binding site and vie for acetate group free from the deacetylation reaction.

The best examples of short chain fatty acid are VPA (valproic acid) and sodium butyrate which are under clinical trials. [46]

*Valproic acid* is used as anti-convulsant and mood-stabilizing agent. But now it is introduced as pan-HDACi which is in the third phase of clinical trial for the treatment of cancer viz. cervical or ovarian. It shows significant therapeutic effect either alone or in combination therapy. [47, 48]
*AN-9* is used for chronic NSCLC, lymphocytic and lymphoma malignancies. [49]

**Cyclic Peptides**

Romidepsin belongs to the class of Depsipeptide which is recently in phase-II clinical trials as well as critical trial in cutaneous and peripheral T-cell lymphomas An unprejudiced response was seeing in 10 of 28 evaluable cutaneous T-cell lymphoma effected patients, from an overall response rate of 36%, it comprising 3 and 7 complete and partial responses respectively. Myelotoxicity, nausea, vomiting, and cardiac dysrrhythmias are the some serious side effects. Hematologic and solid malignancies are shown in cancer affected patients, may be treated with (Depsipeptide), which is also in clinical trials as one track or combination therapy. [50]

**Toxicity in clinical trials**

Antitumorus drugs seem to have serious toxicity than any other class of drugs. In few cases, thrombocytopenia, neutropenia, anemia, fatigue, diarrhea is the certain side effects of inhibitors (grade III and IV). By the discontinuation of the (HDAC) drug, some volunteers suffering from thrombocytopenia along with nausea, vomiting, anorexia, constipation and dehydration were also seen.

Inhibitors of HDAC are also carrying some adverse effect like any class of anticancer agents. The inhibitors (grade III and IV) cause certain side effects like thrombocytopenia, neutropenia, anemia, fatigue and diarrhea.[51, 52] In few cases, HDAC causes thrombocytopenia but it can be easily convertible by discontinuation of the drug.[40] Some other side effects were also seen like nausea, vomiting, anorexia, constipation and dehydration. Deaths of the volunteers in the clinical trials have been reported involving HDAC inhibitors. For example, during trials of mocetinostat with critical Hodgkin's lymphoma four patients died, of that two were treatment related deaths.[53] Similarly some other demises were also perceived during clinical trials involving vorinostat, givinostat.[52, 54] Hence, before step into the clinical trials some amendments are necessary to reduce the toxicity of HDAC inhibitors and curtail the cytotoxicity effects in patients.

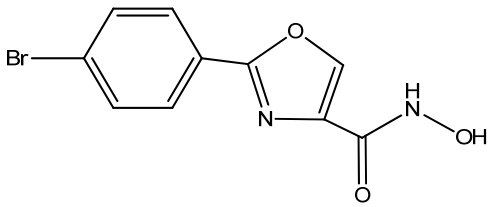
**Approaches towards development of HDAC Inhibitors**

Till date number of HDAC inhibitors have been recognized but are not considered to be competitive inhibitors of histone deacetylases. The enzymes are inhibited by insertion of the same catalytic site as the usual enzyme substrates called competitive-inhibitors. Competitive HDAC inhibitor normally contributes to pharmacophore, which depends upon the crystal structures of enzyme inhibitor (HDAC-like protein comes from Aquifex Aeolicus) complex.

Non-competitive inhibitor selectively disrupts the HDACs interaction with precise DNA binding proteins and some regulatory proteins which might be selectively potent (**Fig. 4**).[12] Alteration of an identified HDACIs is very important to recognize the chemical entity that affects the potency of inhibitor. This is an important initiative for further investigation of a novel chemical compound.

Some of the new histone deacetylase inhibitors with peptoid-based cap groups were synthesized and found to be better selective against HDAC6 isoform than towards other HDAC isoforms (**Fig. 5** [13]). The compounds obtained from this hypothesis has been found to be more active showing extraordinary chemo-sensitizing belongings and remarkable activity against Cal27 and CisR.[13] Selective inhibition of HDAC6 is a promising target nowadays for the wide range of diseases such as neurodegenerative disorders (Alzheimer's disease, Huntington's disease, and Parkinson's disease), cancers and hematological malignancies.

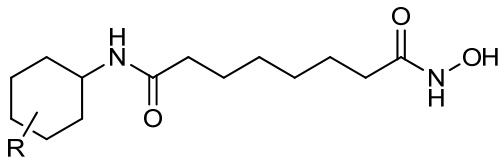
In the line of identification of some selective HDAC6 inhibitors, a biaryl hydroxamate structure was explored without any branching. The heterocycles (thiazole, oxazole & oxadiazole) attached to the hydroxamate showed a huge impact on HDAC6 potency and selectivity. The compound **1** containing oxazole moiety has been identified by Senger and co-workers as potent and selective inhibitors in vitro and in cell cultures.[14]




**(1)**

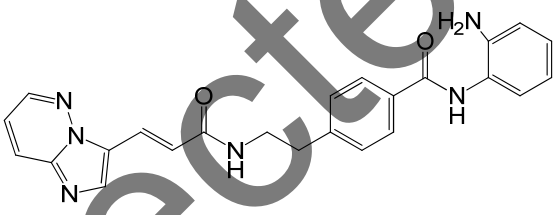
**Zhang et al., (2015)** outlined the synthesis, characterization and biological evaluation of SAHA based derivatives which have greater binding towards HDAC8 than the suberoylanilide

hydroxamic acid. The compound **2** shows pronounced activity while inhibiting the cancerous cell lines of human glioma i.e. MGR2, U251& U373.[15]



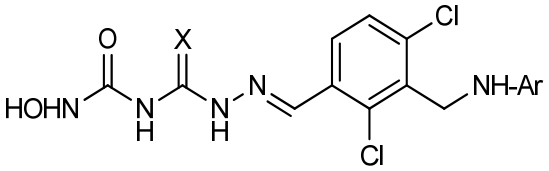
**(2)**

Bicyclic heterocyclic compounds are well known and widely used in medicinal chemistry which always attributes remarkable attention in pharmaceutical industry due to their wide therapeutic values. A series of novel acrylamide derivatives based on the lead compound of MS-275 has been synthesized by Yanyang and his co-workers. The synthesized compounds were quantized for anti-proliferative activities against cancerous cell lines (HCT-116, MCF-7, A549). Furthermore, the compound **3** manifested an adequate pharmaco-kinetic report amid bioavailability in mice which is 76%, are probably deliberated as a novel compound in drug discovery process.[16]



**(3)**

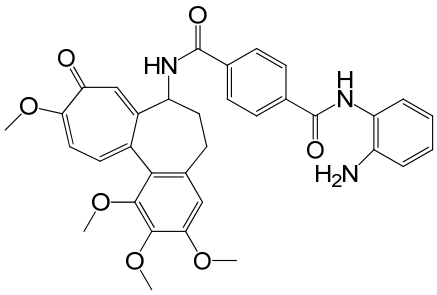
**Chavan et al., (2015)** outlined and synthesized number of derivatives having semi or thio-carbazone moiety containing hydroxamic acid which have average to higher G score. Numerous compounds exhibited potent anti-proliferative effect for MCF7, HCT15 and Jurkat cancer cell line. Compound **4** showed potential activity against colon cancer.[17]



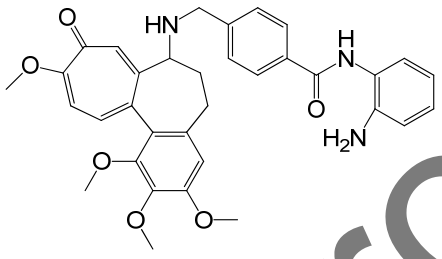
**(4)**

**Zhang et al., (2015)** described colchicine bearing hydroxamate moiety with histone deacetylase inhibitory activity that possesses good effect against histone deacetylases and

tubuline. The compound **5a-b** show modest inhibition of HDAC activity and significant action on cyto-toxicity. [18]

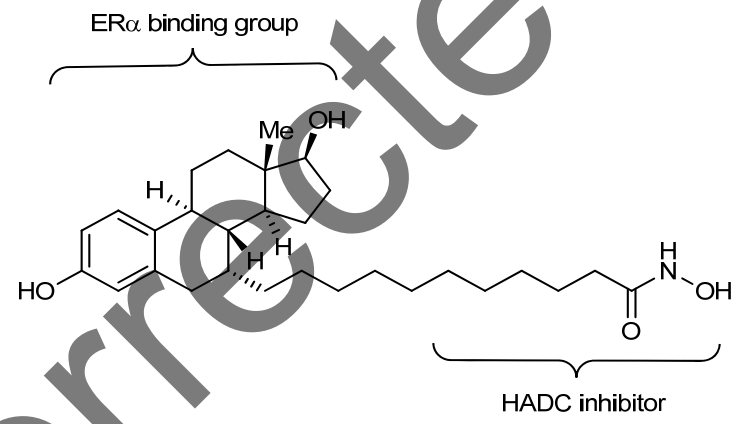


**(5a)**



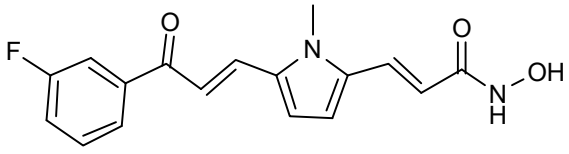
**(5b)**

**Mendoza-Sanchez et al., (2015)** outlined that the fusion of anti-estrogens with known HDACi to obtain more effective anti-proliferative compound for the treatment of breast cancer. The fused compound **6** holds an anti-estrogenic and HDACi activity. The benzamide bi-functional molecule was found to be active for Class I deacetylases (HDAC3) and Class II deacetylases (HDAC6) and potent in nM concentration in breast cancer models.[19]




**(6)**

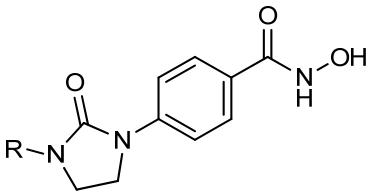
**Fleming et al., (2014)** reported the advanced synthesis and structural modification of MC1568 **7** which were found to be selective for class IIa HDAC inhibitor.[20]




**(7)**

**Cheng et al., (2014)** reported the synthesis of phenyl-imidazolidin-2-one derivatives as selective HDACi. The compound **8** of the series possess remarkable anti-tumor activity against

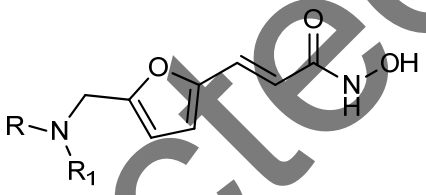
cancer cells lines (HCT-116, PC3 and HL-60) in comparison to SAHA. Also showed major anti-tumor effect in the xenograft model of HCT 116 mice.[21]




R = aryl, alkyl

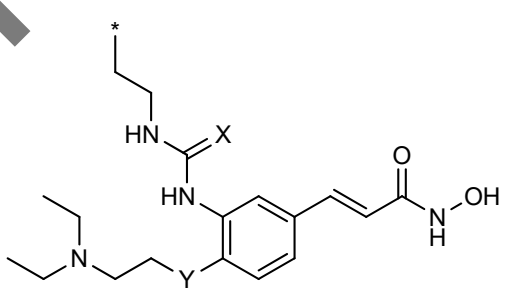
**(8)**

**Feng et al., (2013)** depicted the influence of insertion of branched hydrophobic group e.g. N-hydroxyfurylacrylamide at cap side of HDAC inhibitor and was reported to determine the activity in terms of inhibitions against tumor cell. All the synthesized compounds were reported to have high selectivity towards histone deacetylase 1 and the compound like **9** showed magnificent selectivity next to HDAC6.[22]




**(9)**

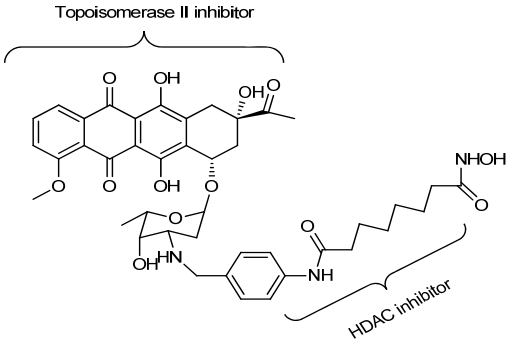
**Ning et al., (2013)** accounted that the substitution of urea/thiourea on disubstituted cinnamic based hydroxmates (**10**) have remarked histone deacetylase inhibitory effect and anti-proliferative activity against tumor cell lines. [23]




**(10)**

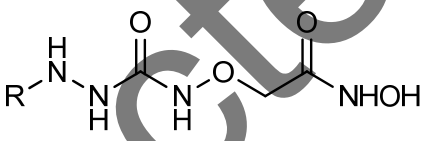
**Guerrant et al., (2012)** reported a bi-functional approach to produce chemoactive agents in a single structural design which have 2-fold activity against HDAC and topoisomerase II.

Results revealed that the compound **11** inhibits both these enzymes with strong hinder capacity against different cancerous cell lines.[24]



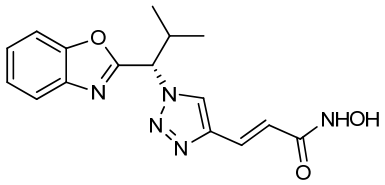

**(11)**

**Marek et al., (2012)** reported a novel series by incorporating an alkoxy-amide linkage in the hydroxamic acid based compounds. Compound **17** exhibited same effects contrasted to SAHA in a pan- histone deacetylase cell based assay and improved cyto-toxic outcome against various cancer cell lines A-2780, Cal-27, Kyse-510, and MDA-MB-231. Compound **12** exerted significant activity against HDAC enzyme and inhibited HDAC4 and 5 in nM concentrations.[25]



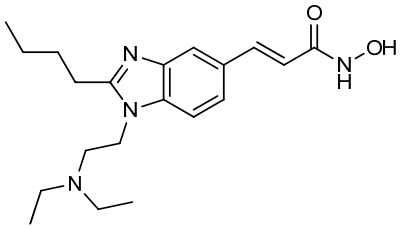
**(12)**

**Hou et al., (2012)** proclaimed a potent chiral compound (NK-HDAC-51) that exhibited potent activity than vorinostat in both enzyme and cell based assays due to the better physicochemical properties e.g. Log-D, solubility, micromole stability of liver($t_{1/2}$), \ stability of plasma ($t_{1/2}$), and apparent-permeability.[26]



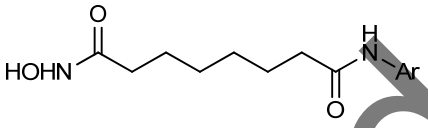
**(13)**

**Wang et al., (2011)** outlined the synthesis of 3-(1, 2-disubstituted-1*H*-benzimidazol- 5-yl)-*N*-hydroxy-acryl-amides HDAC inhibitors. In vivo studies against various tumor models (HCT- 116, PC3, A-2780, MV411, Ramos) showed that compound **14** is highly effective and has very good pharmacokinetics, safety and pharmaceutical properties.[27]



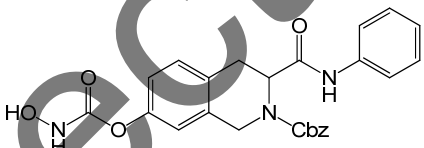
**(14)**

**Chun et al., (2011)** synthesized a series of compound like **15** for anticancer activity and anti-proliferative affect against MCF7, MDA-MB 231, MCF 7/Dox, MCF 7/Tam, SK-OV 3, LNCaP and PC3 human cancer cell lines by the synthesis of suberoylanilide hydroxamate derivatives.[28]



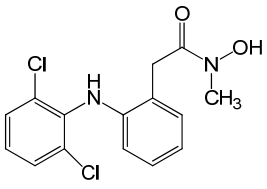
**(15)**

**Zhang et al., (2010)** reported new series of 1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid derivatives for the inhibition of HDACs. The compounds like **16** show potent activity and having better inhibitory activity than Vorinostat. [8]



**(16)**

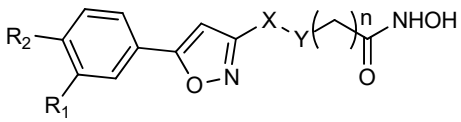
**Koncic et al., (2009)** carefully examined few hydroxamic acid derivatives of NSAIDs **17** and also appraised their antioxidant, radical scavenging activity with allusion to BHA (Butylated hydroxyanisole).[29]



**(17)**

**Kozikowski et al., (2008)** outlined the novel series of hydroxmate based histone deacetylase inhibitor were synthesized followed cyclo-addition method. The compounds like **18**

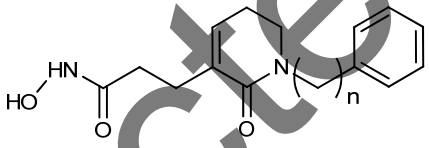
have greater potency against histone deacetylase 6 with IC50 value of 2 picomolars. Few compounds were found to be capability to obstruct the cell growth in pancreatic cancer approx 10-times more effective than vorinostat.[30]




R1 = NHBoc or H
R2 = NHBoc or H
X = CO or CH2
Y = NH or O
n = 4 or 6

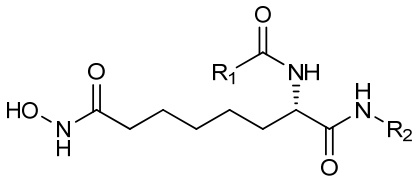
**(18)**

**Kim et al., (2007)** reported that novel δ-lactam based HDAC inhibitors which have various substituted benzyl, bi-aromatic cap groups were prepared through metathesis reaction. Compound **19** showed inhibitory activity against five different human cancer cell lines including (PC3, AC-HN, NUGC3, HCT15, and MBA-MB-231).[31]



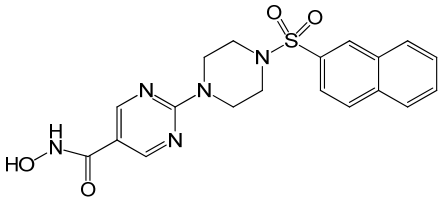

**(19)**

**Kahnberg et al., (2006)** described various derivatives of 2-aminosuberic acid. The compound **31** has an ability to kill a range of tumor cells including MM96L melanoma cells, out of whole compounds. The compound **20** exhibits hyper-acetylation of histones in both normal and cancerous cells, induces p-21 expression, and discriminate the survival of cancer cells to a non-proliferating phenotype.[32]



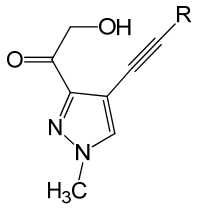

**(20)**

**Angibaud et al., (2005)** described a series of novel pyrimidyl-5-hydroxamic acids for HDAC inhibition. Moreover, amino-2-pyrimidinyl can be used as a linker to provide enzymatic potency to HDAC inhibitors.[33]



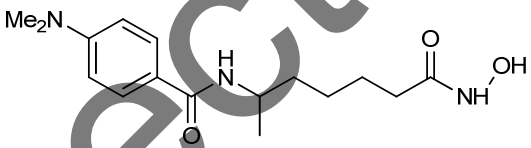
**(21)**

**Mshvidobadze et al., (2004)** developed a variety of pyrazolo hydroxamic acid molecules which showed greater efficiency against HDAC enzyme.[34]



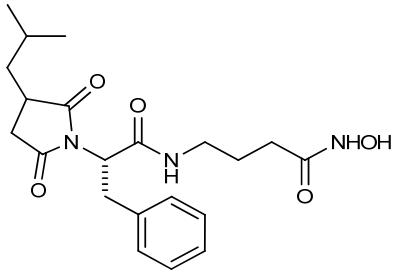
**(22)**

**Tourwe et al., (2003)** reported the potent amide type histone deacetylase inhibitors and molecular modeling confirms the flexibility of the linker chain of the compound **23**, which is important for the orientation of the dimethyl-amino-benzoyl group in the enzyme.[35]



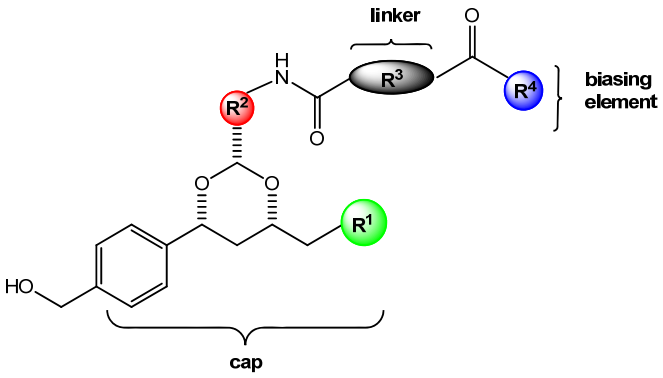
**(23)**

**Curtin et al., (2002)** outlined synthesis and evaluation a series of succinimide hydroxamic acid, which were prepared and evaluated for HDAC inhibition and anti-proliferation. Compound **24** were found to be more potent.[36]



**(24)**

**Sternson et al., (2001)** synthesized series of potent compounds like **25** having 1, 3-dioxane moiety that showed HDAC inhibitory activity.[37]




**(25)**

## Conclusions

There is an enormous expansion for the management of cancer due to which probability of survival of the cancer patients has been improved significantly. Although there are various medication for the treatment of cancer but seems to be still ineffective and creates a challenge for the research groups working in this arena to develop safe, effective and agents with improved therapeutic index. Histone deacetylases inhibitor (HDACI), a new category of anti-cancer agents, exerts innumerable biological effects *viz.* stimulation of cell differentiation, cell-demises, cell-cycle arrest, and bringing on of autophagic cell death.

Development of specific HDAC inhibitor with an enhanced therapeutic index leads to successful target accomplishment that proceeds to increase their efficacy. Additionally, recent clinical studies postulate that the inhibitor of HDAC enzyme responds to both hematological and solid tumor malignancies. Low therapeutic range is the one of major drawback of existing HDAC inhibitors. Inhibitor of HDAC enzyme either used in monotherapy and combination therapy with different targeted agents. Combination therapy is more viably successful then monotherapy because it's used as chemotherapeutic and bio-therapeutic agents in tumors having least toxicity and better clinical outcomes.

The present review highlights the SAR of various histone deacetylases inhibitors synthesized across the globe, which will be helpful for designing new more potential agents. Special attention to be found on the existing synthesized medicinal compound in past few years,

and their therapeutic application that will be helpful for the future advancement. Apart from cancer, HDACIs are presently used in different remedial areas such as neurodegenerative disorder, cardiovascular disease, liver fibrosis, retinal degenerative disease, regulation of immune response, anti-inflammatory, conjunctivitis, asthma etc. Also we have tried to summarize the current developments in the structural scaffold of HDACIs such as surface recognition site, linker region and metal binding moiety. The recent summation by various research groups has been incorporated to understand the advancement of potential inhibitors.

**Conflict of interest**

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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