Turk J Pharm Sci 2019;16(1):101-114
DOI: 10.4274/tjps.75047

REVIEW

Histone Deacetylase Inhibitors: A Prospect in Drug Discovery

Histon Deasetilaz İnhibitörleri: İlaç Keşfinde Bir Aday

Rakesh YADAV*, Pooja MISHRA, Divya YADAV

Banasthali University, Faculty of Pharmacy, Department of Pharmacy, Banasthali, India

ABSTRACT

Cancer is a provocative issue across the globe and treatment of uncontrolled cell growth follows a deep investigation in the field of drug discovery. Therefore, there is a crucial requirement for discovering an ingenious medicinally active agent that can amend idle drug targets. Increasing pragmatic evidence implies that histone deacetylases (HDACs) are trapped during cancer progression, which increases deacetylation and triggers changes in malignancy. They provide a ground-breaking scaffold and an attainable key for investigating chemical entity pertinent to HDAC biology as a therapeutic target in the drug discovery context. Due to gene expression, an impending requirement to prudently transfer cytotoxicity to cancerous cells, HDAC inhibitors may be developed as anticancer agents. The present review focuses on the basics of HDAC enzymes, their inhibitors, and therapeutic outcomes.

Key words: Histone deacetylase inhibitors, apoptosis, multitherapeutic approach, cancer

ÖZ

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: Histon deasetilaz inhibitörleri, apopitoz, çoklu tedavi yaklaşımı, kanser

INTRODUCTION

In recent years, immense progress has been made in the management of cancer, due to which the life expectancy of cancer patients has been improved remarkably. Cancer is represented by inappropriate 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 histone deacetylase inhibitors (HDACIs) are the emerging ones.[2] Various reports in the literature revealed that certain histone deacetylase (HDAC) family members are aberrantly expressed in several tumors and have a nonredundant function in controlling the hallmarks of cancerous cells. They are classified into two types, i.e., Zn-dependent (class I and class II) and nicotinamide adenine dinucleotide (NAD)-dependent (class III) enzymes. Currently, researchers around the globe are paying more attention to the modification of the Zn-dependent portion of the histone family. At present, there are a total of 11 HDAC family members identified on the basis of their similarity chain (Figure 1).[3,4]

*Correspondence: E-mail: rakesh_pu@yahoo.co.in, Phone: 9694891228 ORCID-ID: orcid.org/0000-0002-8932-5076
Received: 24.06.2017, Accepted: 25.01.2018

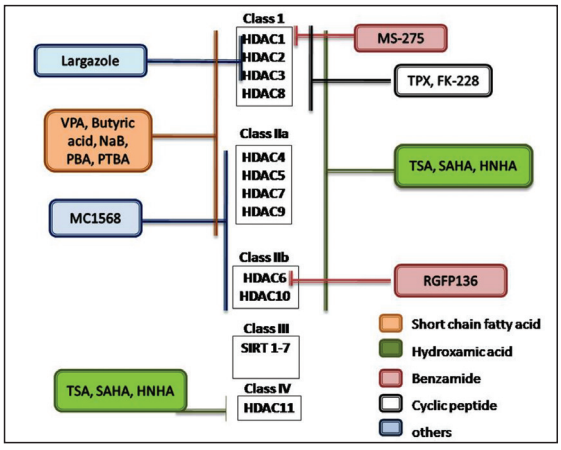


Figure 1. Schematic representation of different histone deacetylase and inhibitors

HDACs are enzymes that catalyze the deacetylation of lysine remnants located at the *N*-terminal of several protein substrates, such as nucleosomal histones. Histone acetylation has an important role in gene expression. Histone acetyl transferases and HDACs are the two types of enzymes that 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. HDACIs have attracted significant interest recently for the treatment of cancer as well as of other human disorders.[6]

A number of HDAC inhibitors have been reported to date that cause tumor cell growth arrest at doses that are apparently nontoxic and appear to be very selective.[1] HDACIs consists of three defined structural parts of an ideal pharmacophore, i.e., (a) recognition cap group (b) hydrophobic linker, and (c) the zinc-binding group (Figure 2).[7,8] Earlier, HDACIs highlighted the alteration of the surface recognition site (capping group) and the zinc ion binding group.[5] Some selective HDACIs help in identifying the specific position of the HDAC protein responsible for cancer. This prospective identification by HDACIs plays an important role to improve the therapeutic profile of new generation HDACIs. In addition to changing the metal binding site, the hydrophobic site is also varied, concentrating on modifying the linker site by varying unsaturation and adding a ring (e.g., aryl, cyclohexyl) inside the series,[9] but still selective and potent HDACIs are yet to be investigated.

On the basis of chemical structures and enzymatic activities, HDACIs are (Figure 3)[10] chemically classified as *hydroxamates* (vorinostat, panobinostat, givinostat, quisinostat, abexinostat, belinostat, tefinostat, resminostat, pracinostat), *benzamides* (entinostat, mocetinostat, chidamide), *aliphatic acids* (valproic acid), and *cyclic peptides* (romidepsin).[11] These HDACIs possess specific structural components that trigger diverse functions like interruption in the cell cycle, angiogenesis, and immunomodulation by acting on histone and non-histone proteins.[9] A large number of HDACIs originate from natural

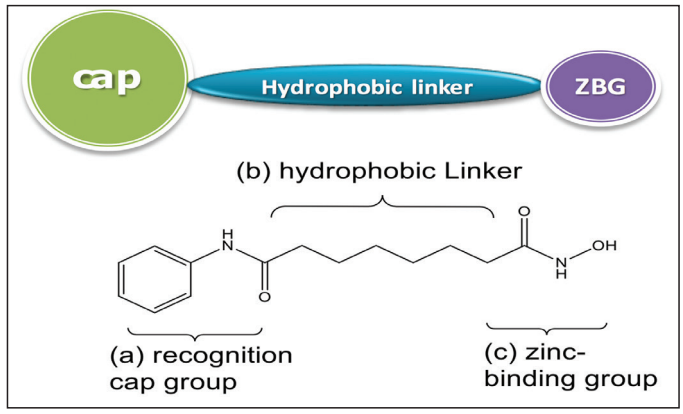


Figure 2. Pharmacophore requirements for histone deacetylase inhibitors

sources and show substantial effects against cancer cells. Some examples of natural HDACIs are given in Table 1.[12-14]

Food and Drug Administration approved and clinical trial drugs

Vorinostat, romidepsin, belinostat, and romidepsin are HDACIs that are approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma (CTCL). More than 80 HDACIs drugs are under clinical trial at present and 11 of them are particular for solid and hematological tumors. Single and combination drugs for the treatment of other types of cancer are shown in Table 2.[3]

Hydroxamic acids

A number of HDACIs have been identified and some are under clinical trial with a hydroxamic acid scaffold for the treatment of various types of cancer. The hydroxamic acid-based drug molecule consists of three defined structural parts of an ideal pharmacophore, i.e., (a) recognition cap group, (b) hydrophobic linker, and (c) zinc-binding group. HDACIs act by binding to the cap bearing amino group, a linker with 4-6 carbon unit and zinc binding group for the inhibition of enzyme.[15]

Trichostatin A is the first hydroxamate-based HDACI that was isolated from *Streptomyces hygroscopicus* to inhibit HDACs. Only the R-isomer of Trichostatin A was found to be active against HDACs.[16]

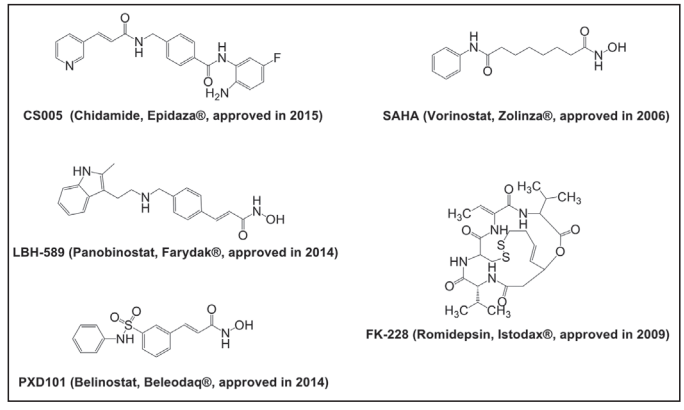
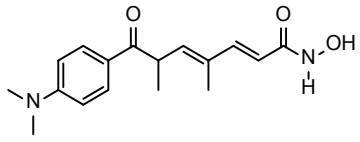
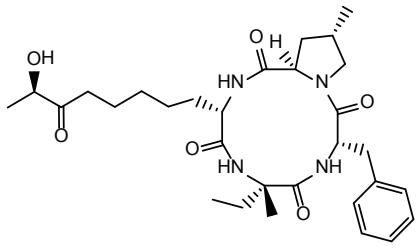
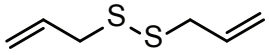
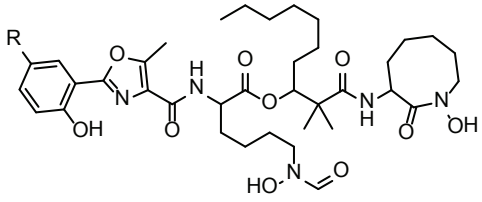
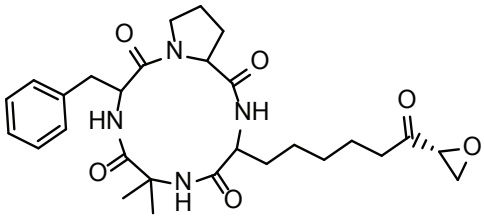
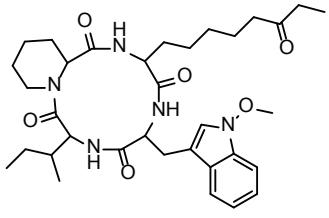
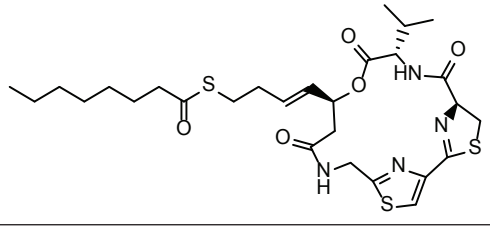
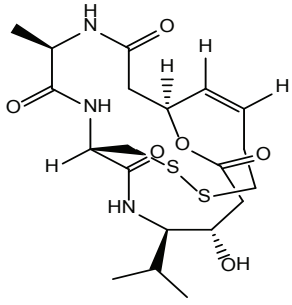


Figure 3. Some of the approved histone deacetylase inhibitors

Table 1. Naturally occurring HDACIs

S. no.	Name	Structure	Natural source	Activity
1	TSA		*Streptomyces hygroscopicus* (actinomycete)	Anticancer
2	FR235222		*Acremonium* sp.	Human leukemia cell inhibition (U937) proliferation and arrest cell cycle (G1 phase)
3	Diallyl disulfide		*Allium sativum*	Antitumor activity
4	Amamistatin (A) R= OMe, (B) R= H		*Nocardia asteroides*	Anticancer
5	Chlamydocin		*Diheterospora chlamydosporia*	Antitumor
6	Apicidin		*Fusarium* sp.	Antitumor
7	Largazole		Cyanobacterium *Symploca* sp.	Antitumor
8	Spiruchostatin A		*Pseudomonas*	Anticancer

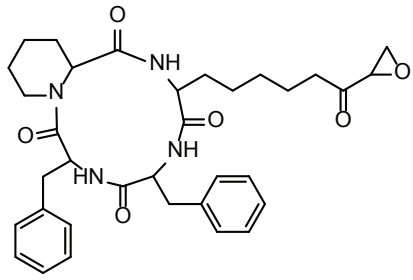
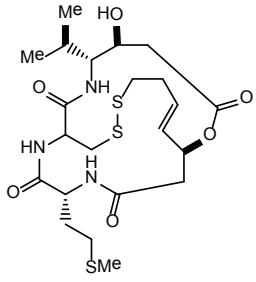
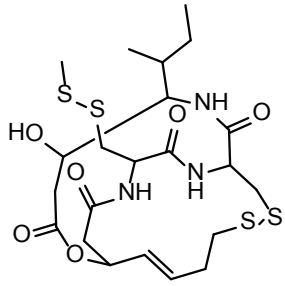
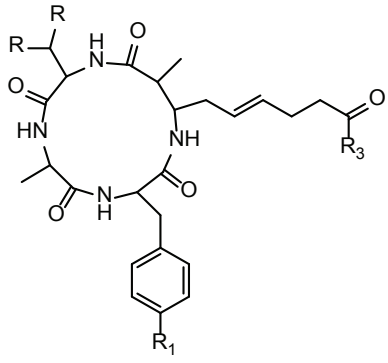
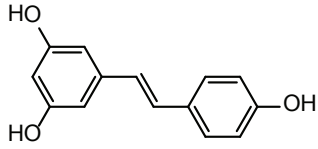
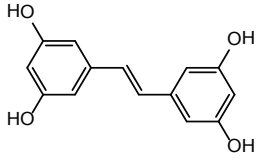
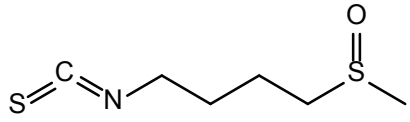
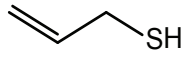
9	Trapoxin A		*Corollospora intermedia*	Anticancer
10	Burkholdac A		*Burkholderia thailandensis*	Antiproliferative activity
11	Thailandepsin A		*Burkholderia thailandensis*	Anticancer and antitumor activity
12	Azumamide (A) R/R1/R2 = CH3/H/NH2; (B) CH3/OH/NH2; (C) CH3/OH/OH; (D) H/H/NH2, (E) CH3/H/OH		Marine sponge *Mycale izuensis*	Anticancer and effective for mammalian solid tumor
13	Resveratrol		*Vitisvinifera/ cyanococcus*	Anticancer activities
14	Piceatannol		*Cyanococcus*	Anticancer activities
15	Sulforaphane		*Brassica oleracea*	Effective against prostate, colon, and breast cancer
16	Allyl mercaptan		*Allium sativum*	Anticancer

Table 2. Various HDACIs in clinical trials

			Hydroxamic Acid Based	
HDACIs	**HDAC specificity (class)**	***In vitro* efficacy**	**Combination therapy**	**Types of cancer**
Vorinostat (SAHA)	1 and 2	Nanomolar	Temozolomide plus radiation	Glioblastoma multiforme (GBM)
			Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP)	Peripheral T-cell lymphoma (PTCL)
			X	Gastro-intestinal (GI)
			Whole brain radiation	Brain metastasis
			5-Fluorouracil (5FV)/Leucovorin (LV)	Refractory colorectal and prominent tumors
			Hydroxychloroquine	Modified tumors
			NPI-0052	Pancreatic and lung malignancy
			Velcate®	Multiple myeloma
			5-fluorouracil (5FV)	Metastatic-colorectal
Beleodaq (Belinostat)	1 and 2	Micromolar	X	Malignant pleural mesothelioma
			X	Epithelial and microcapillary ovarian malignancy
			X	Thymus epithelial cancer
			X	Myelodysplastic syndrome (MDS)
			Paraplatin	Platinum resistant ovarian malignancy
			Carboplatin plus Paclitaxel	Ovarian cancer
			X	Acute myeloid leukemia (AML)
			Cisplatin + doxorubicin + cyclophosphamide	Thymus epithelial tumor
PCI-24781 (Abexinostat)	1 and 2	Nanomolar	X	Complex solid cancers
			Pazopanib	Metastatic solid cancer
			Cisplatin + radiation	Naso-pharyngeal carcinoma (NPC)
SB939 (Pracinostat)	1, 2, and 4	Micromolar	X	Myelofibrosis (MF)
			X	Complex solid tumors
			X	Intractable solid tumors
Resminostat	1 and 2	Micromolar	X	Complex solid tumors
			X	Relapsed/refractory Hodgkin's lymphoma (HL)
			Sorafenib	Advanced hepatocellular carcinoma (HCC)
			X	Colorectal carcinoma
Givinostat (ITF-2357)	1 and 2	Nanomolar	X	Myeloproliferative neoplasms (MPN)
			Hydroxycarbamide	Polycythemia vera
Panobinostat	1 and 2	Micromolar	X	Small cell lung malignancy (SCLC)
			X	Myelofibrosis (MF)
			X	Solid tumors
			X	Cutaneous (T-cell) lymphoma
			X	Relapsed or refractory Hodgkin's lymphoma
			X	Myelodysplastic syndrome (MDS)
CUDC-101	1 and 2	Nanomolar	X	Modified solid tumors

Table 2. Continued

Benzamide Based				
HDACIs	**HDAC specificity (class)**	***In vitro* potency**	**Combination**	**Cancer types**
MGCD0103 (Mocetinostat)	1 and 4	Micromolar	X	Leukemia
			X	Myelodysplastic syndrome (MDS)
			X	Chronic lymphocytic leukemia (CLL)
			X	Modified solid malignancy
			X	Relapsed Hodgkin's lymphoma
MS-275 (Entinostat)	1	Micromolar	CRA (13-cis retinoic acid)	Modified solid malignancy
			Erlotinib	Non-small cell lung cancer (NSCLC)
			Exemestane	Breast malignancy
			X	Refractory solid malignancy and lymphoma
CI994 (Tacedinaline)	1	Micromolar	X	Modified solid malignancy
Short Chain Fatty Acid Based				
HDACIs	**HDAC specificity (class)**	***In vitro* efficacy**	**Combination therapy**	**Cancer types**
Valproic acid	1	Micromolar		Refractory/central nervous system (CNS) tumors
				Neuro-endocrine tumors (NET)
			Avastin	Colorectal, prostate, and breast melanoma
			Decitabine	Non-small cell lung cancer (NSCLC)
			(S-1)	Pancreato-biliary
			Apresoline	Solid malignancy
Phenylbutyrate	1 and 2	Micromolar	X	Refractory solid tumor/lymphoma
			X	Persistent brain tumor
			Vidaza®	Acute myeloid leukemia or MDS
			Vidaza®	Prostate malignancy
			Vidaza®	Non-small cell lung cancer (NSCLC)

Vorinostat (*N*-hydroxy-*N*'-phenyl-octanediamide), marketed under the name Zolinza® by Merck, was the one of the first HDACIs permitted for the treatment of CTCL by the FDA, in 2006.[17] Vorinostat hinders all classes of HDAC proteins (I, II, and IV), except class III HDAC, which is NAD^+ dependent.[18,19]

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

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

Abexinostat (PCI-24781) has been reported as a potent hydroxamate-based HDACI having a wide spectrum of anticancer activity. It is used alone or together with proteasome inhibitors in the treatment of neuroblastoma cell lines.[25] Abexinostat is used with the usual chemotherapy agents, or is used for different types of carcinomas, e.g., tissue soft-tissue sarcoma (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 for the treatment of ovarian cancer, CTCL, thymoma or thymic carcinoma, and myelodysplastic syndrome. This drug showed remarked effects in single or combined therapy.[27]

CUDC 101 is multitarget inhibitor of enzymes and receptors like HDAC, tyrosine kinases, epidermal growth factor receptor, and human epidermal growth factor receptor-2 and it possesses 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 affected patients.[29] The drug has also been tested for modified solid tumors[30] but yielded no promising results. The drug also showed greater effectiveness in children with refractory solid tumors.[31]

Resminostat prevents cell growth and robustly induces apoptosis in multiple myeloma cell lines in small μm concentration.[32] This drug shows a significant effect when dispensed in combination with other drugs (melphalan, bortezomib).[33] In phase II clinical

trials, it showed positive effects in Hodgkin's lymphoma and was also evaluated for higher colorectal malignancy.[34]

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

Tefinostat or CHR-2845 (cyclopentyl 2-((4-(N[1]hydroxyoctanediamido) cyclohexyl) methylamino)-2-phenylacetate) comes under the hydroxamic acid category used as a particular substrate for hCE-1 (intracellular carboxyl-esterase), whose expression is limited to cells of the family of monocytes/macrophages. It is a monocyte or macrophage focused HDACI that is cleaved to an active acid and has significant effects towards myeloid leukemia. The phase I clinical trial of the drug showed remarkable effects on hematological malignancies and lymphoid tumors.[36]

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

Benzamide derivatives

This is another class of HDACI having 20 amino anilide moiety which targets specifically class I HDACs. They bind to zinc-chelating moiety for the interaction with the catalytic Zn2+ in HDACs' active site.[39]

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

Mocetinostat (MGCD0103) is an isotype of HDACI 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 (in 2015) that showed potential effects in the treatment of pancreatic cancer.[45]

Short chain fatty acids

The chemical class of short chain fatty acids has been also introduced as HDAC inhibitors. Their mode of action is based on the presence of a COOH group covering the acetate release channel with a Zn binding site and they vie for the acetate group freed from the deacetylation reaction. The best examples of short chain fatty acids are valproic acid and sodium butyrate, which are under clinical trial.[46]

Valproic acid is used as anti-convulsant and mood-stabilizing agent. Recently it was introduced as a pan-HDACI in the third phase of clinical trials for the treatment of cancer, i.e., cervical or ovarian. It shows significant therapeutic effects either alone or in combination therapy.[47,48]

AN-9 is used for chronic NSCLC and lymphocytic and lymphoma malignancies.[49]

Cyclic peptides

Romidepsin belongs to the class of depsipeptides, and has recently been tested in phase-II clinical trials as well as critical trials in cutaneous and peripheral T-cell lymphomas. An unprejudiced response was seen in 10 of 28 evaluable CTCL affected patients, from an overall response rate of 36%, comprising 3 and 7 complete and partial responses, respectively. Myelotoxicity, nausea, vomiting, and cardiac dysrhythmias are some of the serious side effects. Hematologic and solid malignancies seen in cancer affected patients may be treated with depsipeptides, which are also under clinical trial in single or combination therapy.[50]

Toxicity in clinical trials

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

Approaches towards the development of HDACIs

Most HDACIs have been recognized but not considered to be competitive inhibitors. The enzymes are inhibited by insertion of the same catalytic site as the usual enzyme substrates called competitive inhibitors. A competitive HDACI normally contributing to the ordinary function of the common model of pharmacophore depends upon the crystal structures of enzyme inhibitor (HDAC-like protein comes from *Aquifex aeolicus*) complex.

Noncompetitive inhibitors selectively disrupting the HDACs' interaction with precise DNA binding proteins and some other regulatory proteins (like 14-3-3 protein) might be potent selective outlines (Figure 4).[55] Alteration of identified HDACIs is important to recognize the chemical entity that affects the potency of inhibitors and is an important initiative for further investigating a novel chemical molecule.

Some of the new HDACIs with peptoid-based cap groups were synthesized and found to be more selective against HDAC6

isoform than towards other HDAC isoforms (Figure 5).[56] The compounds obtained from this hypothesis were found to be more active, showing extraordinary chemo-sensitizing effects and remarkable activity against Cal27 and CisR.[56] Selective inhibition of HDAC6 is a promising target nowadays for a wide range of diseases such as neurodegenerative disorders (Alzheimer's disease, Huntington's disease, and Parkinson's disease), cancers, and hematological malignancies.

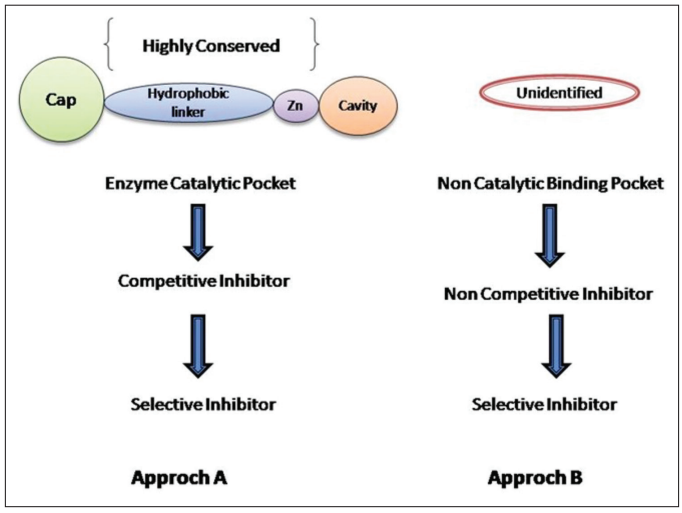


Figure 4. Different approaches for selective histone deacetylase inhibition

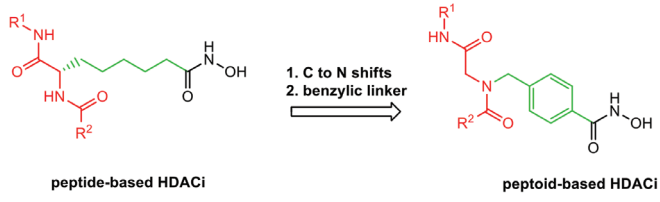
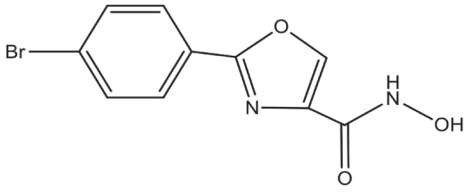


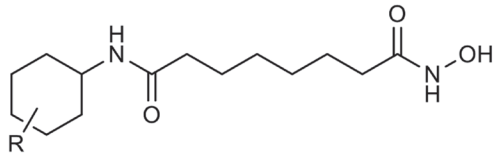
Figure 5. Peptoid-based novel chemical entity effective against HDAC6 isoform

During the identification of some selective HDAC6 inhibitors, a biarylhydroxamate structure was explored without any branching. The heterocycles (thiazole, oxazole, and oxadiazole) attached to the hydroxamate showed a huge impact on HDAC6 potency and selectivity. Compound **1** containing oxazole moiety was identified by Senger et al.[57] as a potent and selective inhibitor *in vitro* and in cell culture.



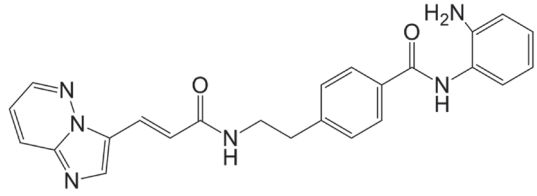
(1)

Zhang et al.[58] outlined the synthesis, characterization, and biological evaluation of suberoylanilide hydroxamic acid (SAHA)-based derivatives with greater binding towards HDAC8 than the SAHA. Compound **2** shows pronounced activity while inhibiting the cancerous cell lines of human glioma, i.e., MGR2, U251, and U373.



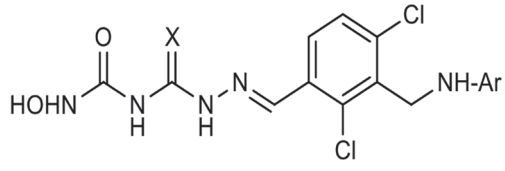
(2)

Bicyclic heterocyclic compounds are well known and widely used in medicinal chemistry, always attracting remarkable attention in the pharmaceutical industry due to their wide therapeutic value. A series of novel acrylamide derivatives based on the lead compound of MS-275 has been synthesized by Li et al.[59] The synthesized compounds were quantized for antiproliferative activities against cancerous cell lines (HCT-116, MCF-7, and A549). Furthermore, compound **3** manifested an adequate pharmacokinetic profile with 76% bioavailability in rats, and can probably be regarded as a novel compound for drug discovery.



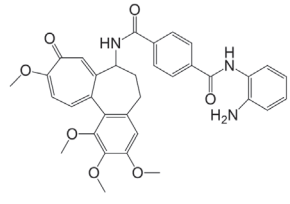
(3)

Chavan and Mahajan[60] outlined and synthesized a number of derivatives having semi- or thio-carbazone moiety containing hydroxamic acid with average to high G score. Numerous compounds exhibited potent anti-proliferative effects for the MCF7, HCT15, and Jurkat cancer cell lines. Compound **4** showed potential activity against colon cancer.

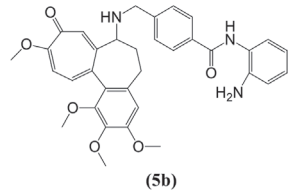


(4)

Zhang et al.[61] described colchicine bearing hydroxamate moiety with HDAC inhibitory activity that possesses good effect against HDACs and tubulin. Compounds **5a-b** show modest inhibition of HDAC activity and significant action on cytotoxicity.



(5a)

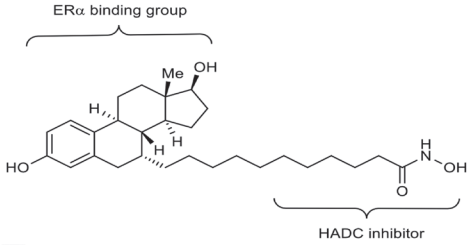


(5b)

(5)

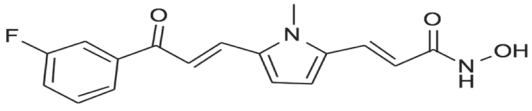
Mendoza-Sanchez et al.[62] outlined the fusion of antiestrogens with known HDACIs to obtain more effective antiproliferative

compounds for the treatment of breast cancer. The fused compound **6** had antiestrogenic and HDACI activity. The benzamide bifunctional molecule was found to be active for class I deacetylases (HDAC3) and class II deacetylases (HDAC6) and was potent in nM concentration in breast cancer models.



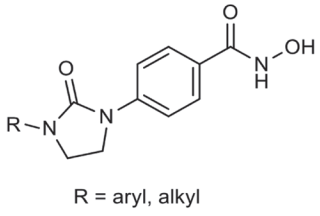
(6)

Fleming et al.[63] reported the advanced synthesis and structural modification of MC1568 (**7**), which was found to be selective for class IIa HDACI.



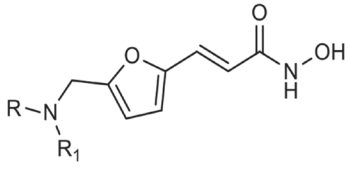
(7)

Cheng et al.[64] reported the synthesis of phenyl-imidazolidin-2-one derivatives as selective HDACIs. Compound **8** of the series possesses remarkable antitumor activity against cancer cell lines (HCT-116, PC3, and HL-60) in comparison to SAHA. It also showed a major antitumor effect in the xenograft model of HCT 116 mice.



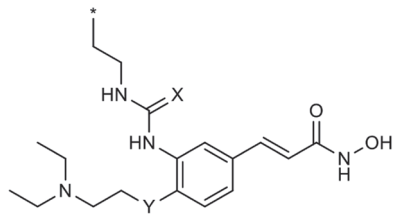
(8)

Feng et al.[65] described the influence of the insertion of a branched hydrophobic group, e.g., *N*-hydroxyfurylacrylamide, at the cap side of HDACI and was reported to determine the activity in terms of inhibition against tumor cells. All the synthesized compounds were reported to have high selectivity towards HDAC1 and the compound like **9** showed magnificent selectivity next to HDAC6.



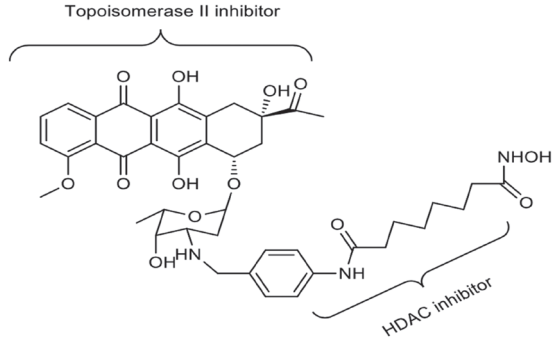
(9)

Ning et al.[66] stated that the substitution of urea/thiourea on disubstituted cinnamic-based hydroxamates (**10**) has a remarkable HDAC inhibitory effect and antiproliferative activity against tumor cell lines.



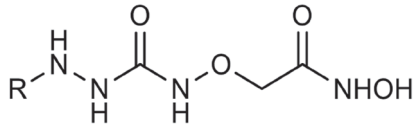
(10)

Guerrant et al.[67] reported a bifunctional approach to produce chemoactive agents in a single structural design that has 2-fold activity against HDAC and topoisomerase II. Results revealed that compound **11** inhibits both these enzymes with strong inhibitory capacity against different cancerous cell lines.



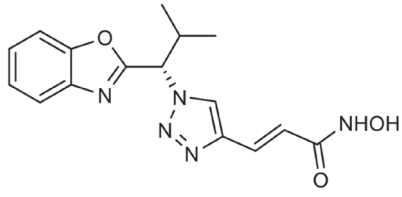
(11)

Marek et al.[68] reported a novel series by incorporating an alkoxy-amide linkage in hydroxamic acid-based compounds. Compound **17** exhibited the same effects contrasted to SAHA in a pan-HDAC cell-based assay and improved cytotoxic 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.



(12)

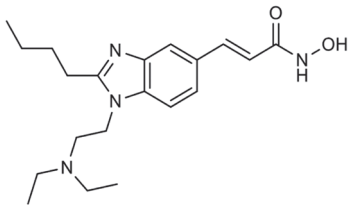
Hou et al.[69] described a potent chiral compound (NK-HDAC-51) that exhibited more potent activity than vorinostat in both enzyme- and cell-based assays due to its better physicochemical properties, e.g., Log-D, solubility, micromole stability of liver ($t_{1/2}$), stability of plasma ($t_{1/2}$), and apparent permeability.



(13)

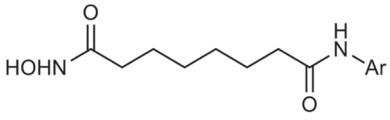
Wang et al.[70] outlined the synthesis of 3-(1,2-disubstituted-1*H*-benzimidazol-5-yl)-*N*-hydroxy-acryl-amides HDACIs. *In*

vivo studies against various tumor models (HCT-116, PC3, A-2780, MV411, and Ramos) showed that compound **14** is highly effective and has very good pharmacokinetics, safety, and pharmaceutical properties.



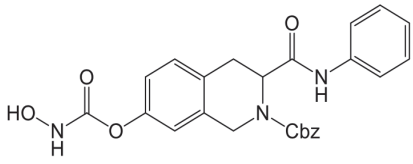
(14)

Chun et al.[71] synthesized a series of compounds like **15** for anticancer activity and antiproliferative effects 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.[71]



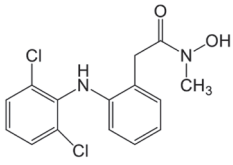
(15)

Zhang et al.[8] reported a new series of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives for the inhibition of HDACs. Compounds like **16** show potent activity and have better inhibitory activity than vorinostat.



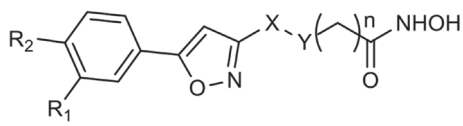
(16)

Koncic et al.[72] carefully examined a number of hydroxamic acid derivatives of NSAIDs (**17**) and appraised their antioxidant, radical scavenging activity with regard to butylated hydroxyanisole.



(17)

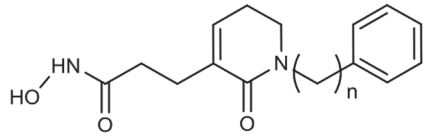
Kozikowski et al.[73] outlined a novel series of hydroxamate-based HDACIs synthesized by cycloaddition method. Compounds like **18** have greater potency against HDAC6 with an IC50 value of 2 picomolar. Some compounds were found to be capable of preventing cell growth in pancreatic cancer approximately 10 times more effectively than vorinostat.



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

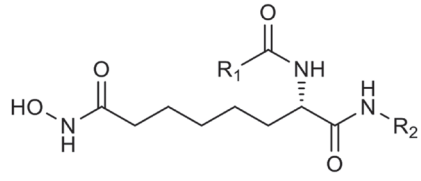
(18)

Kim et al.[74] reported that novel δ-lactam-based HDACIs that 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 (PC3, AC-HN, NUGC3, HCT15, and MBA-MB-231).



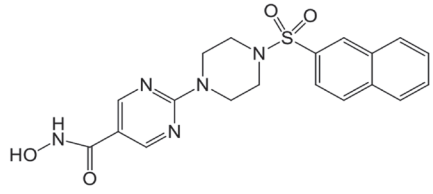
(19)

Kahnberg et al.[75] described various derivatives of 2-aminosuberic acid. Compound **31** has the ability to kill a range of tumor cells including MM96L melanoma cells, out of whole compounds. Compound **20** exhibits hyperacetylation of histones in both normal and cancerous cells, induces p-21 expression, and discriminates the survival of cancer cells to a nonproliferating phenotype.



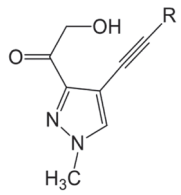
(20)

Angibaud et al.[76] described a series of novel pyrimidyl-5-hydroxamic acids for HDAC inhibition. Moreover, amino-2-pyrimidinylcan is used as a linker to provide enzymatic potency to HDACIs.



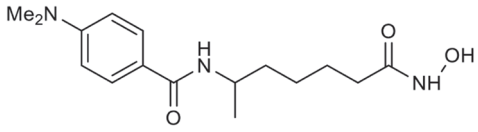
(21)

Mshvidobadze et al.[77] developed a variety of pyrazolohydroxamic acid molecules that showed greater efficiency against HDAC enzyme.



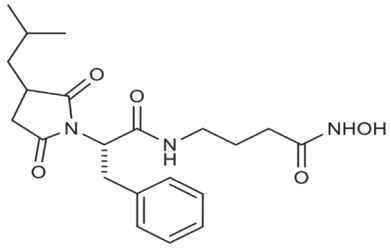
(22)

Van Ommeslaeghe et al.[78] reported potent amide type HDACIs and molecular modeling confirms the flexibility of the linker chain of compound **23**, which is important for the orientation of the dimethyl-amino-benzoyl group in the enzyme.



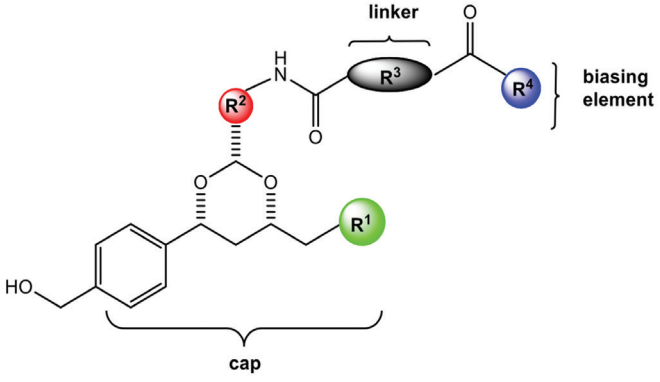
(23)

Curtin et al.[79] outlined the synthesis and evaluation of a series of succinimide hydroxamic acids, which were prepared and evaluated for HDAC inhibition and antiproliferation. Compound **24** was found to be more potent.



(24)

Sternson et al.[80] synthesized a series of potent compounds like **25** having 1,3-dioxane moiety that showed HDAC inhibitory activity.



(25)

CONCLUSIONS

Currently the management of cancer has been improved significantly, and although there are various medications for the treatment of cancer they still seem to be ineffective. Thus it is a major challenge for researchers to develop safe, effective agents with an improved therapeutic index. HDACIs, a new category of anticancer agents, exert innumerable biological effects, i.e., stimulation of cell differentiation, cell demise, cell-cycle arrest, and bringing on of autophagic cell death. Development of specific HDACIs with an enhanced therapeutic index leads to successful target accomplishment that proceeds to increased efficacy. Additionally, recent clinical studies postulate that the inhibitor of HDAC enzyme responds to both hematological and solid tumor malignancies. A low therapeutic range is one of the major drawbacks of existing HDACIs. Inhibitors of HDAC enzyme are used either in monotherapy or in combination therapy with different targeted agents. Combination therapy is more viably successful than monotherapy because it uses chemotherapeutic and biotherapeutic agents having lower toxicity and better clinical outcomes in tumors.

The present review highlights the structure–activity relationship of various HDACIs synthesized across the globe, which will be helpful for designing new potential agents. Special attention was paid to the existing synthesized medicinal compounds over the past few years and their therapeutic application, which will be helpful for future advancement. Apart from cancer, HDACIs are presently used in different remedial areas such as neurodegenerative disorders, cardiovascular disease, liver fibrosis, retinal degenerative disease, regulation of immune response, anti-inflammatory, conjunctivitis, and asthma. We have also 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.

ACKNOWLEDGEMENTS

The authors are thankful to the Vice-chancellor, Banasthali Vidyapith, for providing the necessary research facilities. The financial assistance provided by DST-CURIE, New Delhi, is duly acknowledged.

Conflict of interest: No conflict of interest was declared by the authors.

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