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# *Research progress of histone deacetylase inhibitors*

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***Keywords:*** HDAC, tumors, Histone deacetylase inhibitors, progress.

***Abstract:*** The histone deacetylase (HDAC) is a kind of protease, which plays an important role in the modification of chromosome structure and the regulation of gene expression. However, its dysfunction has been proved to be directly related to the occurrence and development of many diseases (especially tumors). Histone deacetylase inhibitors can interfere with the function of histone deacetylase. Herein, the mechanism of action, advantages and disadvantages of histone deacetylase inhibitors, and the research progress of histone deacetylase inhibitors in tumor therapy are reviewed.

## 1. HAT and HDAC

### 1.1 HAT

Histone acetyltransferases (HAT) are enzymes that acetylate histones. Histone acetyltransferase complexes are involved in many important physiological processes, such as transcriptional activation, gene silencing, cell cycle regulation, DNA replication and repair, and chromosome assembly. [2]

### 1.2 HDAC

So far, 18 subtypes of HDACs have been found. Based on the sequence homology with yeast, 18 HDACs were divided into 4 subfamilies [3]. Class I HDACs include HDAC1, HDAC2, HDAC3 and HDAC8. Class II includes HDAC4, HDAC5, HDAC6, HDAC7, HDAC 9 and HDAC 10. Class III includes sirtuin (SIRT). Class IV includes HDAC11. Class I, II and IV have the same catalytic core region and their functions depend on zinc ions ($Zn^{2+}$). Class I is distributed in the nucleus and mainly represses the transcription of genes. Class II is mainly distributed in the cytoplasm, but can shuttle to the nucleus and is related to information transmission, while class III is quite different from the first two classes, and its activity is not dependent on zinc ions. Instead, $NAD^{+}$ is the catalytic active site, which needs to bind to ADP ribosyl transferase to regulate cell survival, aging and metabolism.

### 1.3 Action mechanism of HAT and HDAC

Histone acetylation/deacetylation modification is one of the key mechanisms of gene transcription regulation [5], which is regulated by HAT and HDAC, respectively. The acetylation of many lysine residues in the amino-terminal region of H3 and H4 histones by HAT reduces the affinity of the whole nucleosome for DNA, promotes chromosome depolymerization and activates transcription. HDAC

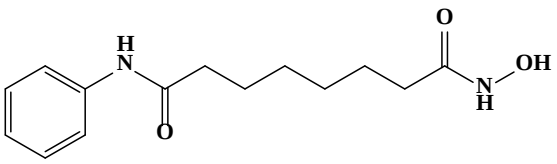
deacetylated histones, which tightly bound to negatively charged DNA, made chromatin compact and coiled, blocked DNA, and inhibited gene transcription. Histone acetylation and histone deacetylation are in a dynamic balance, but once the expression error or dysfunction may lead to the occurrence of tumors.

## 2. HDACi

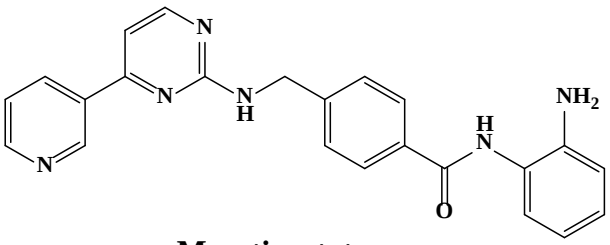
### 2.1 Classification

According to the dependence: Histone deacetylase inhibitors are usually divided into two categories: $NAD^+$ dependent enzymes and $Zn^{2+}$ dependent enzymes. $Zn^{2+}$ dependent proteases include HDACs I, II, and IV subfamilies; The NAD+ -dependent enzymes are mainly of the HDACs III subfamily. Histone deacetylase inhibitors increase the acetylation of histones in cells and increase the expression level of p21 and other genes. Inhibition of tumor cell proliferation and induction of cell differentiation and apoptosis.

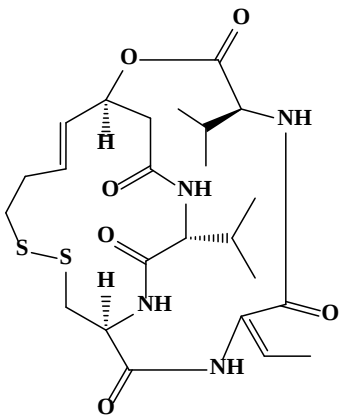
According to the structure, these inhibitors have a common pharmacophore, which consists of three parts: the cap group, ZBG and the linker. According to the type of inhibitor ZBG, the six HDACi were mainly divided into three categories (Figure 1): hydroxamic acids (SAHA); Cyclic peptides (Romidepsin); Benzamides: Mocetinostat




**SAHA**




**Mocetinostat**




**Romidepsin**

*Figure 1: The structure of HDACi*

### 2.2 Hydroxamic acid

Isoalkanoic acid HDAC inhibitors are a class of inhibitors that inhibit the activity of HDACs by chelating $Zn^{2+}$ in the catalytic active center of HDACs with isoalkanoic acid. The hydroxamic acid group is dependent on $Zn^{2+}$, and has inhibitory effect on almost all HDACs of I, II and IV types, and is a type of broad-spectrum HDACi which is thoroughly studied and widely used.

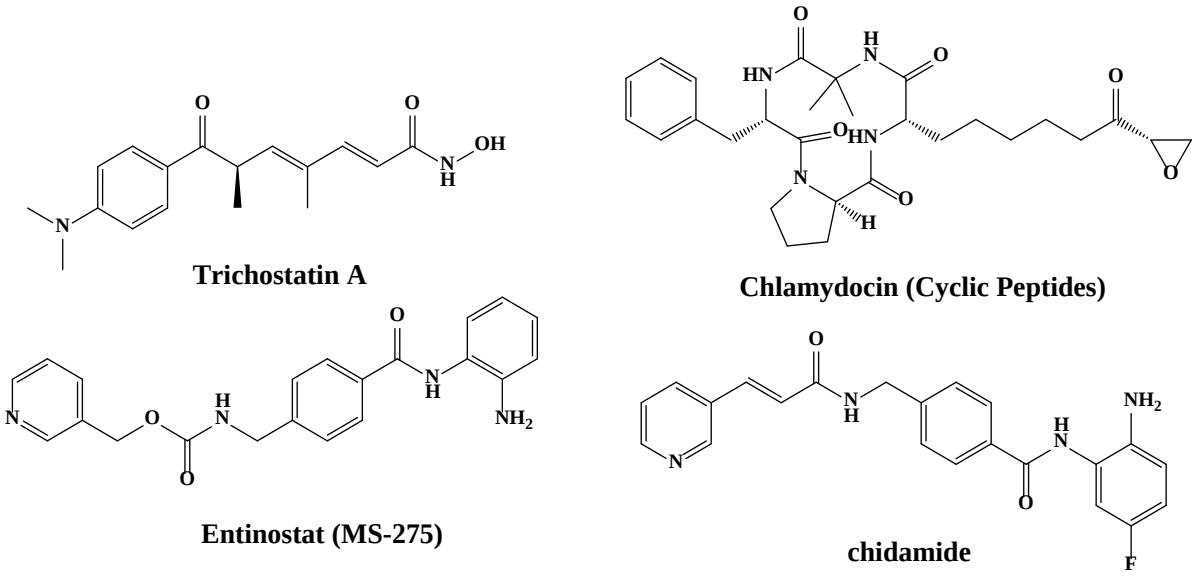



*Figure 2: The structure of Hydroxamic acid*

### *2.2.1 TSA*

TSA is a hydroxamate isolated from actinomycetes and has antifungal activity. Structurally, TSA (figure 2) is similar to SAHA, but TSA has a much stronger inhibitory activity on HDAC. Their major difference is that the TSA linker region contains a diene and an *N*-methyl group.

TSA alters chromatin structure by regulating the acetylation status of histones, and then affects the transcription of related genes, accumulates highly acylated histones, changes the morphology and function of tumor cells, and finally leads to a series of effects such as cell proliferation inhibition, differentiation induction, apoptosis and telomerase activity inhibition. And is less toxic than SAHA, It is internationally recognized as a reliable model to study the effects of acylation on cells, but its mechanism is not very clear.

### *2.2.2 SAHA*

SAHA can directly bind to the $Zn^{2+}$ chelating group at the bottom of the hydrophobic channel [1], which does not require a large number of protein rearrangements and hydrogen bond cleavage of internal ligands, so it belongs to fast HDACi and has good pharmacokinetic properties. SAHA can be used to treat cutaneous T cell lymphoma and induce cell cycle arrest, thereby inhibiting tumor proliferation. It also plays an important role in the prevention of acute graft-versus-host disease. It also has a good synergistic effect with other anti-tumor drugs, but it also shows greater toxicity, such as fatigue, diarrhea, anorexia, dehydration, bone marrow suppression and thrombocytopenia when used in large doses.

## 2.3 Cyclic Peptides

Cyclic peptide HDACIs are the most complex compounds in all inhibitors. The surface recognition structure of macrocycle endows the inhibitors with complex structure, and also ensures that the inhibitors interact with the enzyme molecule more fully. Cyclic peptide HDAC inhibitors act on HDAC enzymes in a manner consistent with hydroxamic acids. HDACIs such as ketone-containing cyclic peptides, hydroxamate-containing cyclic peptides, sulfur-containing cyclic peptides and carboxylic acid-or amide-containing cyclic peptides are widely used in tumor inhibition.

### *2.3.1 Romidepsin*

Romidepsin is a cyclic peptide inhibitor, which modulates the acetylation level of histone H3/H4. Romidepsin also modulates the expression level of PD-L1 through other ways, such as modifying transcription factors. BRD4 can bind to acetylated lysine of histones and regulate gene transcription, thereby regulating the proliferation, apoptosis and MHC-I molecule expression of cancer cells and playing an anti-tumor role.

## 2.4 Benzamides

Such inhibitors are generally less active than the corresponding hydroxamic acids and cyclic peptides. Typical examples are MS-275 and Mocetinostat. Unlike TSA, MS-275, a representative benzamide HDAC inhibitor, targets the two benzene rings of Phe141 and Phe198, which are the narrowest parts of the active pipeline, to prevent the physiological substrate of HDAC (the acetylated side chain of Lys at the nitrogen terminus of histone) from extending to the catalytic center. The 2-amino group forms a hydrogen bond with Tyr91 or Glu92, and the benzene ring in the middle forms a sandwich structure with Phe141 and Phe198. MS-275 is more selective, less toxic, and more tolerable than hydroxamic acid HDAC inhibitors with the mechanism of zinc-ion chelation. Moreover, the unique N-(2-aminophenyl) benzamide pharmacophore contained in the molecule of the drug enables the drug to have stronger HDAC1 and HDAC2 selectivity.

### *2.4.1 Chidamide*

The Chidamide is a selective HDAC1, 2, 3 and 10 inhibitor independently developed in China, and is a benzamide inhibitor, which has been approved for phase III clinical trials for the treatment of advanced peripheral T-cell lymphoma and breast cancer.

## 2.5 Summary of comparison

Based on the comparison of the structure-activity relationship of three kinds of HDACs, it is not difficult to find that benzamide HDAC inhibitors have the most development value. Hydroxamic acids are the most thoroughly studied at present, but their structures are not stable enough, and they target $Zn^{2+}$ and are easy to combine with other proteins containing $Zn^{2+}$ in the human body, so they have many side effects and affect clinical application. The synthetic reaction is a semi-synthetic reaction using natural products as raw materials. The reaction is complex, the yield is low, and there are many by-products, and some of them cause irreversible inhibition of HDAC. Benzamides have the characteristics of relatively simple molecular structure, good action target selectivity, low toxicity and the like.

# 3. Research progress

HDAC inhibitors can treat cancer by increasing acetylation to promote gene expression. HDAC itself participates in the regulation of many genes, which is difficult to monitor effectively [3]. Secondly, some HDACs have high sequence similarity, and sometimes only a certain subtype of HDAC in tumor cells is increased, so more selective inhibitors are urgently needed. The selectivity of the inhibitor has certain challenge. Moreover, most HDACi can bind to other metalloenzymes in addition to $Zn^{2+}$, thus lacking absolute specificity, and they have been found to cause side effects at very small doses. Although inhibitors targeting specific classes of HDACs, such as Romidesine, have been developed, all HDACi lack complete specificity and may cause corresponding adverse reactions. [4] Moreover, long-term use of broad-spectrum inhibitors will cause new balance disorders and easily lead to drug resistance. Based on the above reasons, new HDAC inhibitors are mainly developed in

two directions, the first type is highly selective HDAC inhibitors, and the second type is multi-target-coupled HDAC inhibitors which can play a role of amplification and sensitization. HDAC inhibitors with topoisomerase inhibitors, VEGFR inhibitors, and Platinum-based DNA damage agents have synergistic effects, so the structural combination of HDAC inhibitors and their anticancer drugs is expected to obtain molecules with full therapeutic potential in cancer therapy, but there is also a risk of causing proto-oncogene expression and leading to therapeutic failure. Although existing HDAC-based dual-target inhibitors generally show excellent in vitro activity, However, there are also some defects such as poor activity in vivo and poor selectivity of HDAC subtypes, most of which are still in the stage of clinical research, and there is no dual-target inhibitor based on HDAC on the market.

## 4. Conclusion

In the past decades, with the discovery of a large number of HDAC inhibitors and the continuous strengthening of their research, some have entered the market. At present, there are five HDAC inhibitors that have been approved, namely Vorinostat, Romidesine, Belistat, Pabistat and Chidamide. The previous four were approved by FDA, and the latter was approved by CFDA. A total of 368 drugs have been developed with HDAC as the target, of which 44 have entered the clinical stage. However, most of the currently available HDAC inhibitors are non-isomer selective and suffer from limited efficacy, drug resistance, and toxicity. [2] The development of HDAC inhibitors with good activity and high selectivity has become an important research direction.

For example, Proistat Mesylate, a drug under research by Ling Biology, is a highly selective Class I and Class II B HDAC inhibitor, and its clinical approval application is for recurrent or refractory hematological tumors, mainly B-cell related tumors. At present, Phase I clinical trials have been launched, and it is planned to expand the indications rapidly after the refractory subtype has been listed. Secondly, multi-target-coupled HDAC inhibitors have also received extensive attention from academia and industry, and great progress has been made. Multi-target inhibitors not only avoid the interaction between drugs, but also improve the efficacy of drugs, but it is necessary to coordinate and balance the appropriate parameters, such as the choice of targets, requiring the designed compounds to selectively act on the target. And the inhibitory activity on each target is in a balance and has little difference, thereby reducing the side effects caused by acting on other targets.

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