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Review Article

# Advances in non-Hydroxamate Based Histone Deacetylase Inhibitors as Anticancer Agents

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## ABSTRACT

The carcinogenesis process includes several epigenetic modifications that mainly target the silencing of tumor suppressor genes (TS genes) including ribonucleic acid (RNA) editing, deoxyribonucleic acid (DNA) hypermethylation and histone modification, either by methylation and demethylation, or acetylation and deacetylation. Histone deacetylation is one of the most important epigenetic modifications responsible for cancer development, and thereby, the design of new selective histone deacetylase inhibitors (HDACIs) is a promising chemotherapeutic target. Up to this time, all HDACIs approved are hydroxamic acid based. Yet, hydroxamic acids often show several drawbacks upon administration, such as poor pharmacokinetic properties, poor selectivity, and multiple toxicities. That's why the urge of emersion of a new category of compounds was crucial. Thereby, non-hydroxamate based compounds attracted widespread attention by being a part of several biologically active compounds as a safer alternative for hydroxamate based ones. In this mini-review, we aim to focus on several non-hydroxamate based HDACIs, specifically those used as anticancer agents, and the concept behind their development.

**Keywords:** *Anticancer; epigenetic; histone deacetylase; histone deacetylase inhibitor; non-hydroxamate.*

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## 1. Introduction

### 1.1 Epigenetics

Deregulated epigenetics is one of the major hallmarks of cancer. It refers to altered phenotypes which are inherited resulting from alteration in the gene expression while keeping the genetic sequence intact **[1]**. Exogenous influences and altered environmental conditions can change epigenetic signatures and may give a hint about the origin of different malignancies or neurological disorders **[2, 3]**.

### 1.2 Epigenetics Dysregulation Related to Cancer Development

Several epigenetic dysregulations are incorporated into the cancer development process, for example, RNA editing is a process that could occur to any type of RNA, including microRNA (miRNA) which are short fragments of noncoding RNA. It involves the alteration of the RNA nucleotides either by insertion, deletion, or substitution, or by altering the nucleobases themselves (by, for example, adenosine deaminase acting on RNA (ADAR) enzyme) that results in its aberrant RNA expression. Dysregulation of RNA editing responsible for cellular differentiation is manifested in cancer cells **[4, 5]**.

Hypermethylation of the TS gene promoters

acts as a transcription repressor. It blocks their binding with transcriptional factors. It involves the addition of a methyl group to cytosine nucleotides in the CpG islands, which comprise the promoters of several genes **(Fig.1)**. A class of enzymes known as DNA methyltransferases (DNMT) controls the methylation process with the help of S-adenosylmethionine (SAM) cofactor as a source of the methyl group **[6]**. Moreover, hypermethylation recruits histone methyltransferases (HMTs) and histone deacetylases (HDACs). Consequently, hypermethylation (along with hypoacetylation) induce long term gene silencing of TS gene **[7]**.

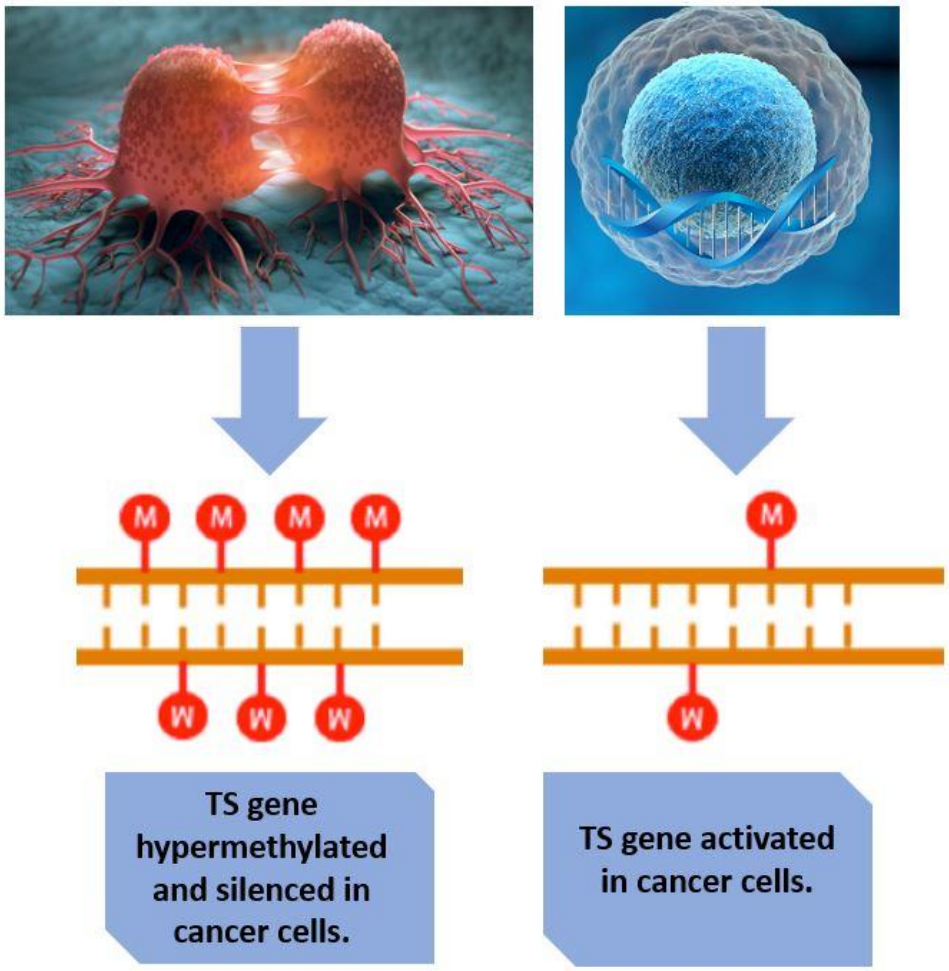


**Fig. 1.** Hypermethylation of TS gene in cancerous cells.

Histone modification involves several processes, among which methylation and demethylation, acetylation, and deacetylation. The balance between each two processes is crucial for homeostasis and any imbalance would contribute to the etiology of cancer development. Methylation and demethylation in lysine have been linked to changes in chromatin structure, thereby influencing DNA accessibility for transcription and gene expression **[8, 9]**.

Histone acetyltransferases (HATs) promote the acetylation of the histone's terminal lysine,

thus leaving the chromatin end loose and susceptible for transcription. On the other hand, HDACs are enzymes that promote the deacetylation of the lysine residue in the histone protein. The latter creates a positive charge that becomes attracted to the negative charge bared by the phosphate group on the DNA hence promoting its wrapping around the histone. As a result, the DNA becomes wrapped preventing its transcription **(Fig. 2)** and, similar to DNA hypermethylation, TS gene will become silenced **[10, 11]**. Recently, several studies stated that HDAC enzymes are overexpressed in cancer cells. For example, HDAC1 is abundantly expressed in gastric and prostate cancer. Colon cancer showed not just the same pattern, but also high levels of HDAC2, HDAC3, and HDAC6 **[12]**. Ovarian cancer showed high expression of all class I isoforms **[13]**.

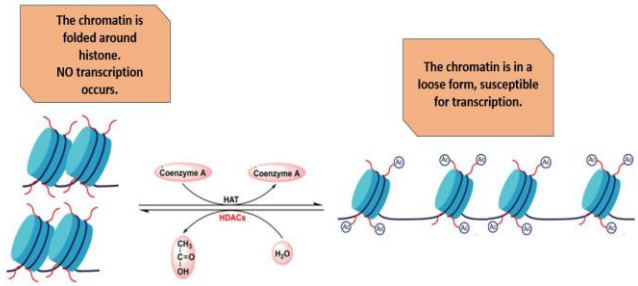


**Fig. 2.** Histone acetylation, deacetylation, and chromatin accessibility.

### 1.3 HDAC Isoforms

There are four categories into which HDAC enzymes fall. One of them is dependent on nicotine adenine dinucleotide ($NAD^{+}$) (class III containing sirtuins from silent information regulator 1 (SIRT1) to SIRT7) and three on zinc. Class I consists of HDAC1-3 and 8. Class IIa comprises HDAC4, 5, 7, and 9 while IIb includes HDAC6 and 10. Class IV includes HDAC11 only **(Fig. 3) [14-17]**.

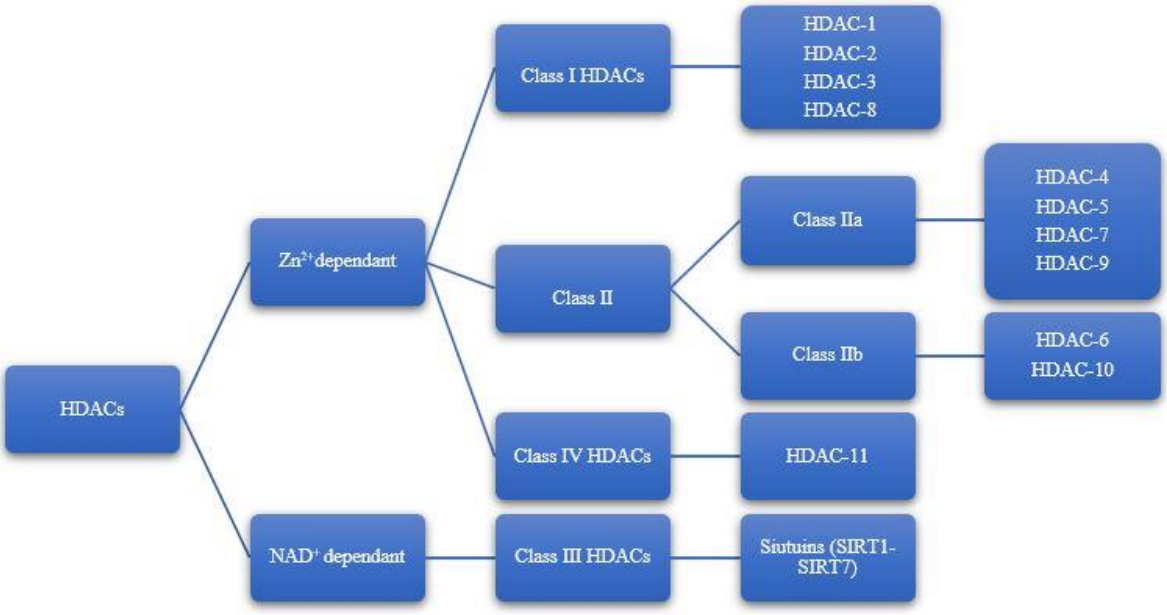


**Fig. 3.** HDAC isoforms classes.

The binding site of all zinc dependent HDACs is nearly the same due to the significant sequence similarity of the residues that make up the catalytic pocket. Its typical structure consists

of a tube-shaped, narrow hydrophobic pocket (about 11 angstrom (Å) deep) that leads to the cavity that house the catalytic machinery (acetate binding cavity) by one side and that connects it to the surface from the other side. It could also be described as a tube composed of a rim, a wall, and bottom regions. Hydrophobic residues mostly line the channel walls. About halfway down the channel, the pocket hits its narrowest point. At the bottom, the pocket widens again to form the polar catalytic core in which the zinc is coordinated **[16]**.

Certain HDAC isoforms have other supplementary pockets, such as side, lower, or foot pocket that would be a perfect target for selectivity.

HDAC1-3 have an internal site pocket that is absent in other classes of HDAC. It acts as a gate for water entrance and acetic acid exit **[18]**.

Class IIa has a lower pocket rather than a foot pocket. That's why a U shaped inhibitor would selectively occupy it **[19]**.

Class IIb HDACs is characterized by its shallow and wide binding channel. Its rim region contains extra binding pockets **[20]**. HDAC6 has even two catalytic sites and sometimes described as a binding site with two pockets, one prefers histones and the other prefers tubulin (tubulin deacetylase (TDAC)) **[21, 22]**.

HDAC11's structure (class IV) is not well understood till nowadays due to the lack of its crystal structure. However, several investigations show that HDAC11 functions as a de-fatty acetylase rather than a deacetylase. Most of HDAC11 selective inhibitors have long-chain fatty acyl groups **[23]**.

## 2. HDAC Inhibitors

HDACIs act as anticancer agents by promoting apoptosis and inducing cell cycle differentiation. That's why they are so called "chromatin-modifying drugs". They could be used alone or along with other anticancer drugs **[10, 24]**.

HDACIs are classified into three distinct categories: short chain fatty acids, cyclic peptides ,and hydroxamates **[25]**.

The first known HDACIs were the "short chain fatty acids" but they showed low potency. One of which was the Food and Drug Administration (FDA) approved antiepileptic drug "Valproic acid" **(Fig. 4)** which was active against class I HDACs, with a half-maximal inhibitory concentration ($IC_{50}$) value of 7.4 mM. Another one of this class was Sodium butyrate, a pan-inhibitor of class I, IIa, and IV **(Fig. 4) [25]**.

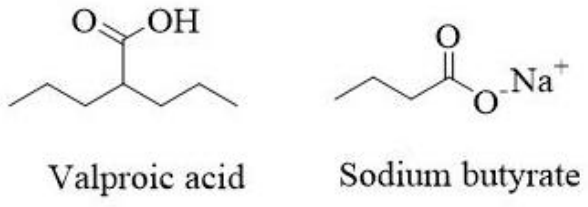


**Fig. 4.** Structure of short chain fatty acids HDACIs: Valproic acid and Sodium butyrate.

The most potent category of HDACIs is hydroxamic acid derivatives. They consist of three major parts:

1-Capping group (makes contacts with the pocket entrance and usually accounts for the selectivity)

2- Linker (spans the tube-like portion of the binding pocket)

3- Zinc binding group (ZBG) which is the hydroxamic acid part (ensures affinity) **[26]**.

The main role of the ZBG is to ensure affinity while the capping group and the linker are responsible for selectivity.

Till nowadays, only 4 HDACIs are FDA approved **(Fig. 5) [10, 11, 27]**.

Due to hydroxamic acid problems like poor

selectivity, poor bioavailability and pharmacokinetics, and production of toxic metabolites, a fourth category of HDACIs with new non-hydroxamates ZBG has been developed **[28, 29]**.

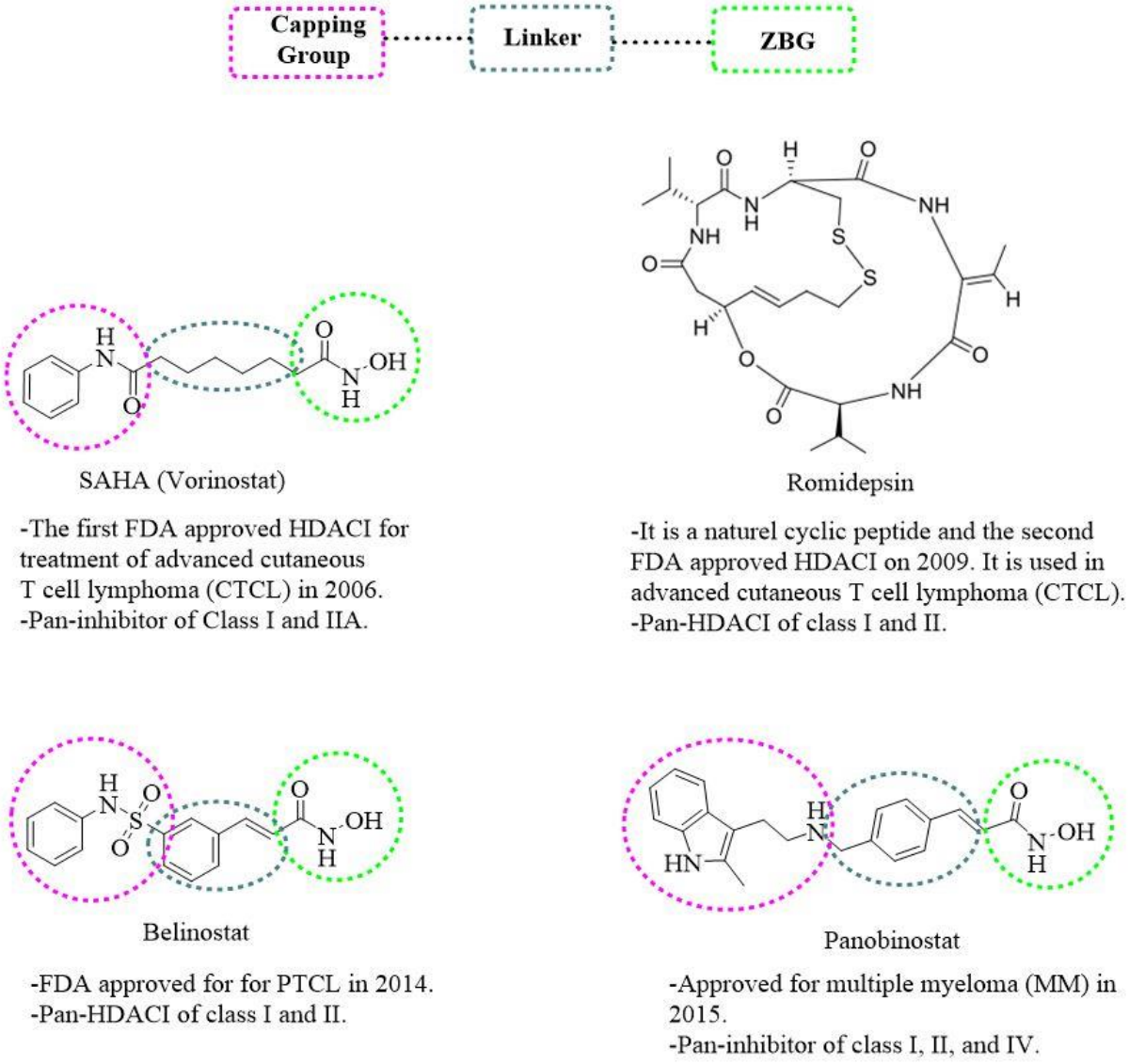


**Fig. 5.** FDA approved HDACIs with illustration of the main scaffolds of the structures (capping group in purple, linker in blue, and ZBG in green).

### 2.1 Non-Hydroxamate Based HDACIs

All the non-hydroxamates HDACIs aimed to share the same general structure of hydroxamates based HDACIs with only different ZBG to overcome the hydroxamates weaknesses.

Despite being less potent, numerous non-hydroxamate ZBGs exhibit isoform preference and can be utilized to maximize isoform selectivity, reduce off-target effects, avoid toxic metabolites, and improve pharmacokinetic characteristics **[30, 31]**. We'll be discussing the recent advances in non-hydroxamate based HDACIs acting as anticancer drugs.

#### 2.1.1 o-Amino Amides Based HDACIs

In 2010, Bressi *et al.* **[32]** synthesized N-(2-amino-5-substituted phenyl)benzamide compounds and evaluated their antiproliferative effect on HCT116 cancer cells. They also investigated their HDAC2 inhibition and used the results to explore its foot pocket. Several compounds showed time-dependent binding kinetics. Those time-dependent binding kinetics depend on two factors:

1- The amino benzamides' unbound form has an internal hydrogen bond between the ortho $NH_2$ and the carbonyl. Upon binding, some molecules lose this intramolecular bond to bind to the receptor. Then, according to *Le Chatelier's* principle, other molecules start to do the same till we reach an equilibrium with the bound and unbound molecules. At this equilibrium, the final $IC_{50}$ will be reached.

2- As we mentioned, since the foot pocket of HDAC2 is larger compared to other members of class I, as the size of the substituent increases (it will reach the equilibrium slower, but the formed complexes will also dissociate slowly), it helps in the selectivity, till a point where the size increase will hinder the entrance of HDAC2. Compound (**1**) **(Fig. 6)** is an example of the optimal size and is used as a co-crystallized ligand with HDAC2 enzyme in protein data bank (PDB) (3MAX) **[32]**.

In 2020, *Nepali et al.* **[33]** conducted a research focusing on the structural improvement of Entinostat (MS-275) and Chidamide **(Fig. 7)** in order to provide more effective antiproliferative medicines. Compound **(2) (Fig. 7)** was found to be more effective than MS-275 and Chidamide in suppressing the growth of triple-negative breast cancer cells MDA-MB-231 ($IC_{50}$= 1.48 mM), MDA-MB-468 ($IC_{50}$= 0.65 mM), and liver cancer cells HepG2 ($IC_{50}$= 2.44 mM). In three leukemic cell lines, K-562, KG-1, and THP-1, it demonstrated more cytotoxicity ($IC_{50}$= 0.33 mM) in comparison to the well-known HDACI Vorinostat. Furthermore, it was discovered to be just as virulent in the gastric cell lines that are resistant to HDACI (YCC3/7) as in those that are susceptible to it (YCC11). This suggests that it may be able to overcome HDACI resistance. With $IC_{50}$ values of 0.108, 0.585, and 0.563 µM, it showed significant inhibitory effects on HDAC1, 2 and 3 isoforms, specifically on HDAC1 **[33, 34]**.


**Fig. 6.** Structure of compound (**1**) showing the ZBG in green.

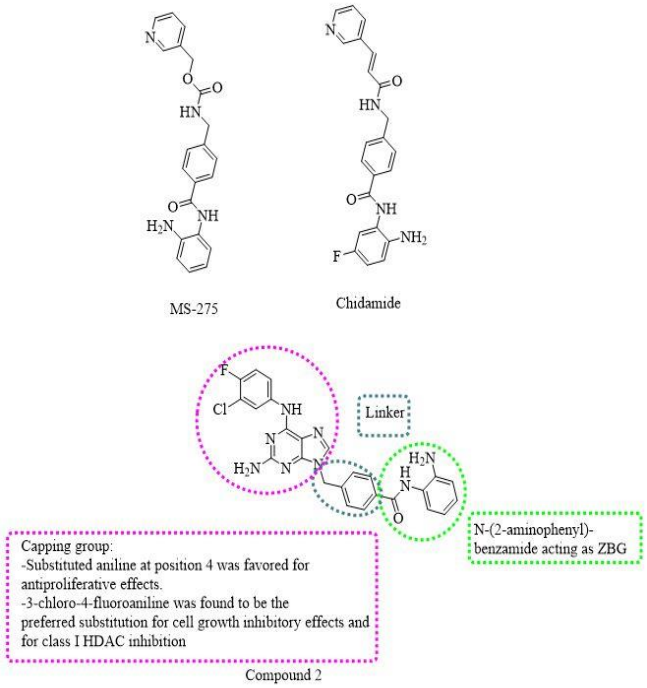


**Fig. 7.** Structure of MS-275, Chidamide, and compound **(2)** showing its main scaffold features**.**

In 2021, Routholla *et al.* **[35]** published a series of novel linker-less benzamides. The most potent HDAC3 inhibitor **(3) (Fig. 8)** with an $IC_{50}$ of 560 nM was having a 6-quinolinyl moiety as the cap group. It showed 46-fold selectivity for HDAC3 over HDAC2 and 33-fold selectivity for HDAC3 over HDAC1 and had much less cytotoxic effects on normal cells with antiproliferative effects on several cancer cell lines. In addition, it triggered cell cycle arrest in B16F10 cells at the G2/M phase of the cell cycle and induced apoptotic cell death in the Annexin-V/FITC-PI assay **[35, 34]**.

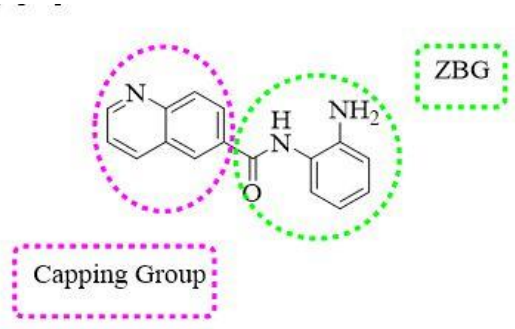


**Fig. 8.** Structure of the linker-less compound **(3)**.

### 2.1.2 α-Ketoamides Based HDACIs

For example, in 2002, Abbot laboratories designed hundreds of electrophilic ketone-based compounds, including α-ketoamides based HDACIs, yet none was specifically claimed. The capacity of these substances to inhibit partly purified HDAC enzymes that were taken out of K562 human erythroleukemia cells was examined (K562 has HDAC1, 2 expressed in abundance). The $IC_{50}$ values of the best compounds ranged from 10 nM to 100 nM. Those are 2 examples of the designed compounds **(4** and **5) (Fig. 9) [36]**.

In 2003, Abbot laboratories also designed new scaffolds containing α-ketoamides as an alternative to hydroxamic based inhibitors. Yet since the alpha ketoamides are readily subjected to metabolism by their conversion into alcohol greatly declining the cellular activity, several structural modifications were conducted to the linker. The best achieved ones were the having meta-amide linked compounds. Further modifications were then conducted on the aryl capping group. The final compound **(6) (Fig. 9)** produced sub-micromolar inhibition of cellular growth and nanomolar inhibition (9 nM) against the isolated fluorescence-based mixture of HDAC1 and 2 enzymes from nuclear extraction of K562 erythroleukemia cells. Though it was still short-lived, it also showed notable anti-tumor effects in vitro and in vivo tumor models. At a concentration of 50 μM, there was an H4 hyperacetylation like that produced by Vorinostat **[37]**. This concludes that the transient concentration obtained was enough to produce the desired antitumor effect **[37]**.

In 2013, Adegboyega Oyelere and Berkley Gryder **[38]** published a patent about several aryl hydantoin based HDACIs intended to treat and/or prevent prostate cancer. They used several ZBGs, among which was 2-ketoamide **(7) (Fig. 9)**. The antiproliferative activity was tested on prostate cancer cell lines. Unfortunately, shortness of study was encountered since detailed data about the activity of each compound, docking studies, or the inhibited HDAC isoforms were not mentioned **[38]**. Similar to Vorinostat and MS-275, those synthesized α-ketoamides didn't show selectivity between HDAC isolated isoenzymes (HDAC1/2, 3, 4/3, and 6), didn't inhibit the TDAC domain and, as a result, didn't accumulate acetylated tubulin on cellular level **[21]**.

In 2014, EŞİYOK *et al.* **[39]** published several synthesized aryl butenoic acid derivatives, including morpholine amide derivatives as ZBG and a linker having a double bond. When tested on HDAC8 isoenzyme against the well-known HDACI Sodium butyrate, the majority of the synthesized compounds demonstrated superior inhibition. Compound **(8)**

**(Fig. 9)** was the most successful candidate as HDACI when tested using in vitro fluorometric assay ($K_i$ in μM= 1.86) and in docking studies **[39]**.

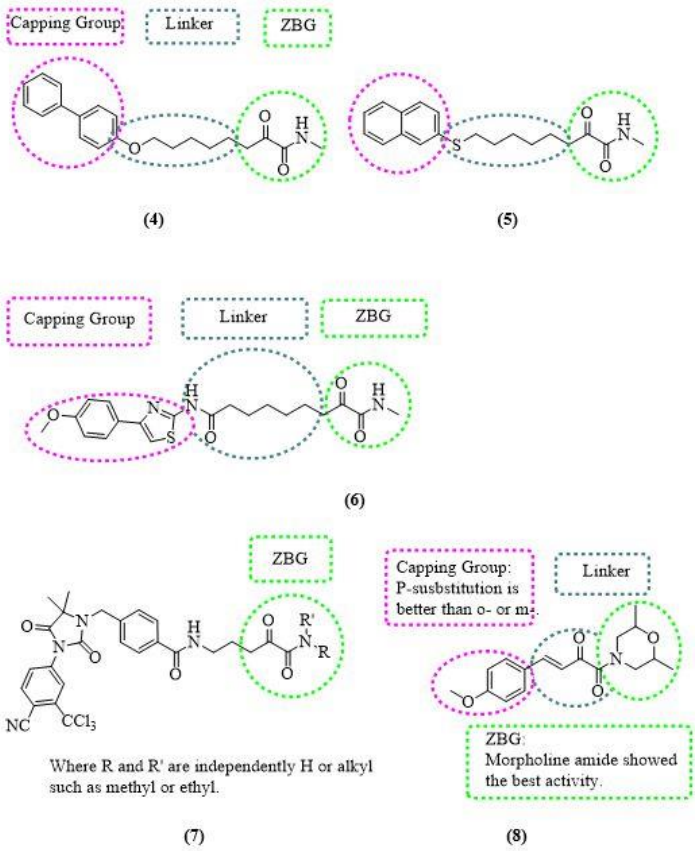


**Fig. 9.** Structure of compound **4, 5, 6, 7,** and **8** (the α-ketoamide based HDACIs) with illustration of the main scaffolds of the structures (capping group in purple, linker in blue, and ZBG in green).

### 2.1.3 Chalcone Based HDACIs

In 2015, Zhou *et al.* **[40]** developed *de novo* reaction-mechanism-based inhibitor β-hydroxymethyl chalcone (**9**) **(Fig. 10)**. The latter has a special time-dependent selective inhibition on HDAC2. This time dependent selectivity can be attributed to the "tandem reaction time-dependent tight-binding kinetics" mechanism, caused by the subsequent dynamic equilibrium of the intramolecular nucleophilic attack reaction (the formation of [E•I]′ complex). Meanwhile, such a time-dependent inhibition effect is much smaller for β-hydroxymethyl chalcone in HDAC1. β-Hydroxymethyl chalcone showed almost 20-fold isoform-selectivity against other members of class I. Another reason behind this selectivity is that the position of one of the β-hydroxymethyl chalcone is more extended than, for example, that of the MS-275 (phase II clinical class-I specific inhibitor) knowing that the foot pocket in HDAC2 is slightly deeper compared to HDAC1 **[40]**. Then, based on Zhou *et al.*'s **[40]** findings, Mohamed *et al.* **[41]** designed a series of chalcone based inhibitors of HDAC2, but the ZBG was o-aminobenzamide group, and tested their anticancer activity against three human cancer cell lines (HCT-116, MCF-7, HepG2). Compound (**10**) **(Fig. 10)** showed the most potent activity with $IC_{50}$ of 7.17±2.01, 12.99±2.99, and 3.02±0.81 towards HepG2, MCF-7, and HCT-116 respectively. Its ability to bind to HDAC2

enzyme was tested through docking **[41]**.

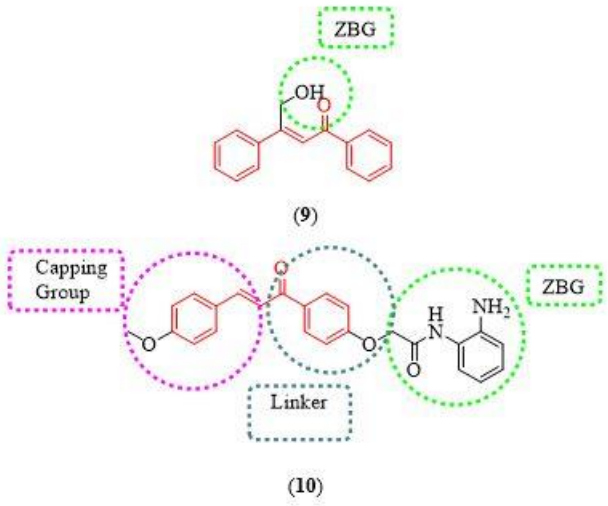


**Fig. 10.** Structure of compound **9** and **10** showing its main scaffold features.

### 2.1.4 Oxime Based HDACIs

In 2011, Botta *et al.* **[42]** synthesized several oxime-containing compounds **(11) (Fig. 11)** having a structure related to Vorinostat, aiming to identify a potential novel binding element for the zinc in the HDAC catalytic site. Even though the novel compounds' overall activity range is less than SAHA inhibition values, it showed higher activity against many HDAC isoforms. Furthermore, the novel α-oxime amide derivatives target particular isoforms in each class of HDACs rather than selecting between class I and class II HDACs, as previously reported for their hydroxamic acid equivalents **[42]**.

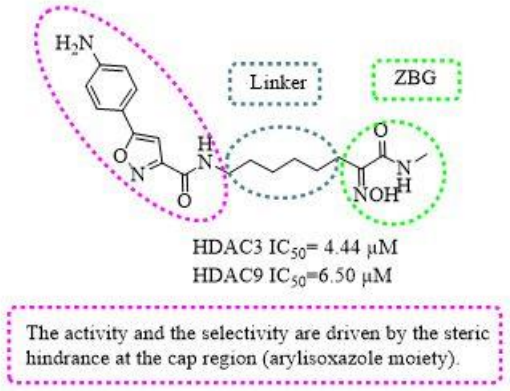


**Fig. 11.** Structure of compound **(11)** showing its main scaffold features**.**

In 2015, another series of Vorinostat analogs, including the shown below compounds **(12, 13, 14) (Fig. 12)** in which hydroxamic acid moiety is replaced by aziridin-1-yl oxime group, was synthesized as anticancer agents. Some of them showed high antiproliferative activity against human HT1080 fibrosarcoma (HT1080, $IC_{50}$ 0.3–7.7 μM) **[43]**.

Finally, other non-hydroxamate ZBGs like thiols, mercaptoacetamides, ketones, carboxylic acids, hydrazides, thiazolidinediones, etc., were thoroughly mentioned in recent reviews **[34, 44]**.

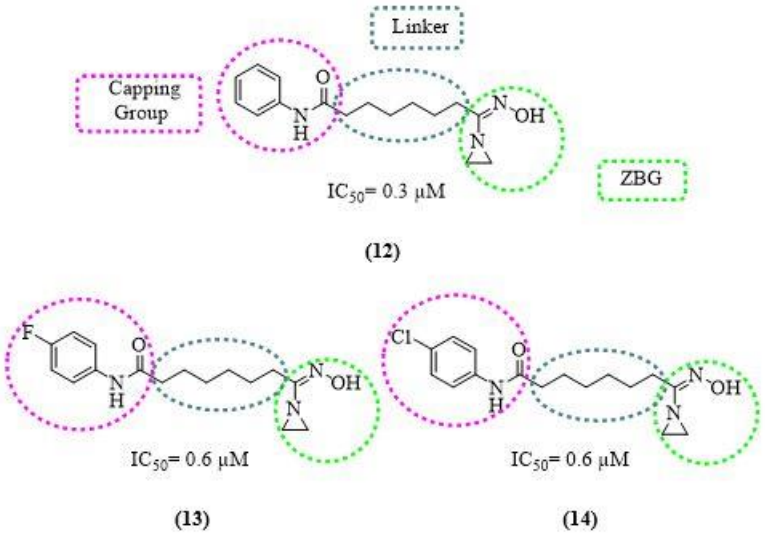


**Fig. 12.** Structure of compound **12, 13** and **14** with illustration of the main scaffolds of the structures (capping group in purple, linker in blue, and ZBG in green)**.**

## Conclusion

Being overexpressed in several types of cancer, histone deacetylases represent a promising target for recent anticancer drugs. Most HDACIs have hydroxamic acid as the zinc binding group owing to its strong ability to chelate zinc ion in a bidentate mode. Yet, despite their potency, they are characterized by several side effects being non-selective and having very poor pharmacokinetics. That's why, novel series of non-hydroxamate based compounds including several groups like amino amides, ketoamides and chalcone were synthesized and their HDAC inhibitory effect was tested.

## Declarations

### Consent to publish

All authors have read and agreed to the published version of the manuscript

### Ethics approval and consent to participate

Not applicable.

### Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

### Conflict of Interest

The authors assert that there are no conflicts of interest.

### Funding Statement

The author(s) received no specific funding for this work.

### Authors Contribution

The first draft of the manuscript was written by Nadine Wafik Nabih, and all authors commented on previous versions of the final manuscript. All authors read and approved the final manuscript.

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