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Recent Perspectives of Anticancer Histone Deacetylase Inhibitors

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Abstract

Histone deacetylases (HDACs) are common targets for cancer therapy as they are expressed in many forms of cancers; several research studies have been introduced discussing the design of small molecules that target this abnormal epigenetic changes developed by HDACs in chromatin. In the past 10 years, HDAC inhibitors have emerged as important agents of interest in clinical trials for several types of cancers and other diseases. Due to the recent availability of a number of HDACIs into the market as effective anticancer agents (like vorinostat, belinostat, panobinostat, romidepsin, chidamide and pracinostat), HDACIs are considered one of the promising targeted anticancer agents. The current review highlights the most recent chemical modifications of HDACIs including different caps, linkers and zinc binding groups and interestingly the dual acting or multi-targeted HDACIs.

Key words
Anticancer, HDACIs, Hydroxamic acids, Multi-targeted HDACIs

1. Histone deacetylases (HDACs)

1.1. HDACs overview

Histone deacetylases **(**HDACs) have received great attention in the research area of epigenetics. Acetylation by HATs transfers an acetyl group and neutralizes the positive charge of lysine residues in histone tail resulting in loosen histone–DNA interactions and allow access of transcription factors to DNA. The stimulatory effect of HATs on gene expression is reversed by HDACs, which remove an acetyl group from the terminal amino group of lysine residue leaving a positive charge, that tightly interact with the negative charge of DNA, promote chromatin condensation and thereby repress transcription and induce gene silencing. [1–3] Thereby, HATs are defined as co-activators and the HDACs are co-repressors. [4] Consequently, a higher level of acetylation induces apoptotic cell death, whereas a higher level of deacetylation promotes gene repression and suppression of tumor suppressor genes (p53, p21, p27) resulting in carcinogenesis. In normal cells, there is a balance between HATs and HDACs activity. On the contrast, there is an imbalance between histone acetylation / deacetylation in cancer cells through over-expression of HDACs or suppression of HATs that result in oncogene activation, tumor progression and tumor suppressor gene inactivation. [1] The aberrant expression and/or activity of HDACs and HATs have been associated with the development of different tumors therefore, HDACs were found to be over-expressed in a wide variety of human cancers. [5,6]

1.2. Classes of HDAC enzymes

Eighteen HDACs have been identified and grouped into four classes (class I, II, III and IV) based on the homology to their yeast *Rpd3*, *Had 1* and *Sir2*. [7] Classical HDACs include Class I, II, and IV and comprise 11 family members, whereas class III members are called sirtuins. Classical HDACs and sirtuins differ in their catalytic mechanisms; Classical HDACs are Zn^{2+} dependent enzymes with a Zn^{2+} ion as essential co-factor at its active site that can be inhibited by Zn^{2+} chelating histone deacetylase inhibitors, while, class III enzymes that called sirtuins requiring NAD+ as an essential cofactor. [8–15] The class I HDACs comprises HDAC1, 2, 3 and 8 that are found to be expressed and localized mainly in the nucleus of the cells and having sequence homology with the yeast *Rpd3* (reduced potassium dependency 3). [16] On the other hand, class II HDACs is further divided into two subclasses: class IIa which includes HDACs 4, 5, 7, and 9 and class IIb which includes HDACs 6 and 10. [17] Class II HDACs have homological similarity with yeast gene *Hda 1*, they are primarily localized in the cytoplasm but can shuttle between the nucleus and the cytoplasm. [18] Moreover, class III HDACs or sirtuins (SIRT1-7) have homologous similarity with yeast *Sir2* (silent information regulator 2). They are localized in nucleus, mitochondria and cytoplasm. [19] The only member of class IV is HDAC11 which is found in both the nucleus and the cytoplasm. [20] It has a structural similarity to class I and II enzymes. [17]

1.3. HDACs and cancer

HDACs are considered as a potential target for regulation of epigenetic aberrance. [21] HDACs reverse the function of HATs by deacetylating core histones. In addition, they regulate non-

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histone proteins, including tumor suppressors, signaling mediators and transcription factors. [22] Most importantly, different HDACs are over-expressed in many cancer cell lines and tumor tissues and also have an important role in tumor development. [23] Individual HDACs regulate tumorigenesis *via* quite diverse mechanisms. Because HDACs induce a range of cellular and molecular effects through modification of histone and nonhistone substrates, HDACs could either repress tumor suppressor gene expression (p21, p53) or regulate the oncogenic cell-signaling pathway. The contribution of HDACs to cancer may not necessarily be related to the level of HDAC expression, because the aberrant activity of HDACs is also common in cancer development. Aberrant expression of classical (class I, II, IV) HDACs has been linked to a variety of malignancies, including solid and hematological tumors. [24] High expression of HDAC1, 2, and 3 are associated with poor prognosis in gastric, ovarian, prostate, lung, breast and colorectal cancers. [25–27] Similarly, over-expression of HDAC6 and HDAC7 has also been found in cutaneous T-cell lymphoma and pancreatic adenocarcinoma. [26] Moreover, HDAC6 is over-expressed in mammary tumors, HDAC8 is overexpressed in neuroblastoma cells and HDAC11 mainly in rhabdomyosarcoma. [27,28] According to the above data, the inhibition of HDACs introduces anticancer activities in many cancer cell lines. Inhibition of HDACs promotes cell differentiation, apoptosis, cell cycle arrest and inhibit angiogenesis in many cancer cells. Hence, HDAC inhibitors are considered as promising targets for the development of new anticancer drugs. [29–31]

2. Histone deacetylase inhibitors (HDACIs)

2.1. HDACIs overview

Histone deacetylase inhibitors (HDACIs) have been emerged as a new class of anti-cancer agents that play important roles in epigenetic regulation of gene expression inducing death, apoptosis, and cell cycle arrest in cancer cells. [32–34] A number of HDACIs with much more potent anticancer effects and diverse structures have been identified; they include natural or synthetic products. [35,36] Recently, many HDAC inhibitors have been clinically validated in cancer patients resulting in the approval of five HDACIs, vorinostat, romidepsin, belinostat and panobinostat by the FDA and chidamide by Chinese FDA for the treatment of cutaneous, peripheral T-cell lymphoma (CTCL, PTCL) multiple myeloma (MM) and acute myeliod leukemia (AML) **(Figure 1)**. [37–45] SAHA, belinostat, and panobinostat are pan-HDACIs since they targeting multiple HDAC isoforms, while romidepsin is a selective one. [46,47] Several new HDACIs are in different stages of clinical development for the treatment of hematological malignancies as well as solid tumors. HDACIs have the potential to be used as mono-therapies or in combination with other anticancer therapies. [35,48] Also, great efforts are exerted to discover novel HDACIs for use as anti-cancer drugs alone or in combination and have isoform selectivity are continuing by researchers. [49]

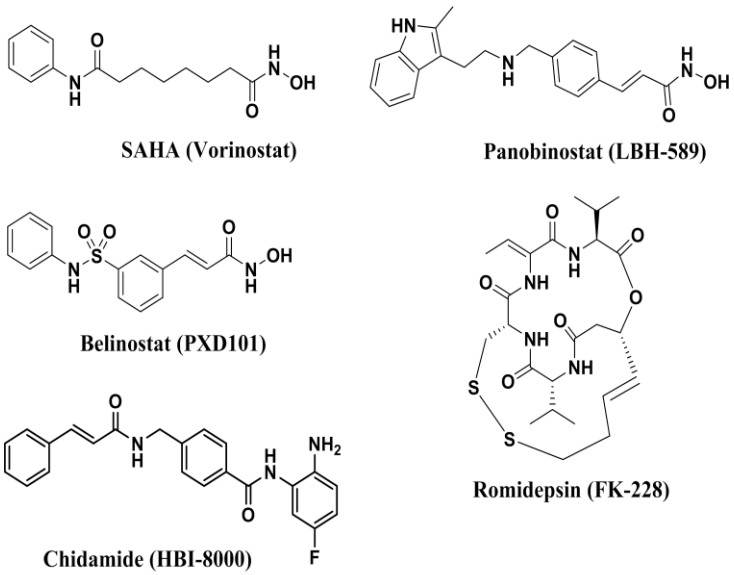


Figure 1: FDA approved HDACIs

2.2. Mechanism of action of HDACIs as anticancer

The HDACIs induce acetylation of histones and non-histone proteins and alter gene expression leading to transcriptional activation of certain genes and repression of others. The anticancer activity of HDACIs is stemmed from their ability to regulate the expression of specific proliferative and/or apoptotic genes. HDACIs induce cancer cell cycle arrest, differentiation; reduce angiogenesis and leading to cell death. [27,50,51]

a) Induction of Cell Cycle Arrest

HDACIs increase expression of cell cycle genes such as p21 (CDK inhibitor), and in addition, inhibit CDK activity via down-regulation of cyclins that eventually induce cell cycle arrest and differentiation. [52–54]

b) Anti-angiogenesis

HDACIs can inhibit tumor angiogenesis via suppression of pro-angiogenic factors, including vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), and up-regulation of p53 that inhibit hypoxia-induced angiogenesis. [55–57]

c) Activation of apoptotic pathways

HDACIs induce apoptosis via both the extrinsic and intrinsic pathways. The extrinsic pathway of apoptosis cause up-regulation of TNF-α that induces activation of caspase 8 and 10, resulting in apoptotic cell death. On the other hand, the intrinsic pathway leads to increase expression of pro-apoptotic proteins including Bim, Bak, Bax, and caspase-3, while the expression of anti-apoptotic proteins such as Bcl-2 is decreased. [58,59]

d) Induction of DNA damage and inhibition of DNA repair

HDACIs activate the DNA damage pathway. They alone do not induce double-strand breaks but synergize the activity of DNA damaging agents to inhibit tumor growth. Moreover, HDACIs

reduce the expression of DNA repair proteins. Reactive oxygen species (ROS) are accumulated, leading to DNA damage after treatment with these agents. [25,51,60,61]

2.3. General Pharmacophore of HDACIs

The known HDACIs share a common pharmacophore. This pharmacophoric model consists of three structural parts named a cap group also named surface recognition moiety (SRM), a hydrophobic spacer (HS) or the linker, and a zinc-binding group (ZBG) **(Figure 2)**. [62–64**]** The cap group linked to an HS through a connection unit (CU). At the end of the HS, a ZBG chelates with the zinc metal and inhibits enzyme activity. Cap group able to interact with the surface of the catalytic tunnel of the enzyme and it is an extremely variable moiety, ranging from a simple benzene ring to a more complex cyclic tetrapeptide. The HS that fits in the narrow hydrophobic channel of the active site is usually with various length linear hydrophobic methylene groups (saturated or unsaturated), aromatic or hetero-aromatic. The ZBG chelates with the zinc metal and the most common ZBGs include hydroxamic acid, [65–72] 2-aminoanilide, [73–75] electrophilic ketones [76] and short chain fatty acids. [77,78] The changes in the cap group, the linker or the ZBG individually can provide selectivity for specific HDAC isoform. [79]

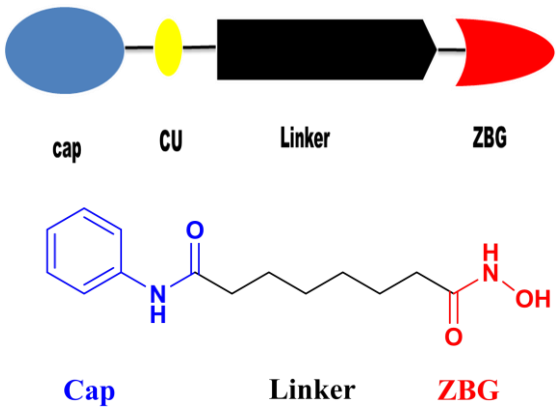


Figure 2: General pharmacophore of HDACIs and the structure of SAHA.

2.4. Classes of HDACIs

HDACIs are classified into different distinct classes based on their ZBG: hydroxamic acids, 2-aminoanilides (benzamides), cyclic peptides, electrophilic ketones, and short chain fatty acids. [35,46,80] These molecules are more or less specific to one/several HDAC enzymes or HDAC classes. The hydroxamates were the first discovered and still being the most potent and popular HDACIs. Cyclic peptides are the most structurally complex class of HDACIs. Benzamides have lower activity than the corresponding hydroxamic acids and cyclic peptides. The compounds in benzamide class are selective and potent inhibitors of Class I HDACs. The short-chain fatty acids are relatively weak inhibitors of the HDACs. [81–84]

Hydroxamic acids

Hydroxamic acid derivatives represent the most popular and potent class of HDACI drugs [85,86]. According to the x-ray crystal structure of trichostatin A (TSA) and SAHA binding interactions with the active site of histone deacetylase-like protein (HDLP), the hydroxamic acid group chelates zinc ion in a bi-dentate fashion through its carbonyl, and hydroxyl groups. Also, three additional hydrogen bonds arise between the carbonyl, the hydroxyl, and the amino groups of hydroxamic acid derivative and Tyr 297, His 132, His 131 of HDLP **(Figure 3)**. [87]

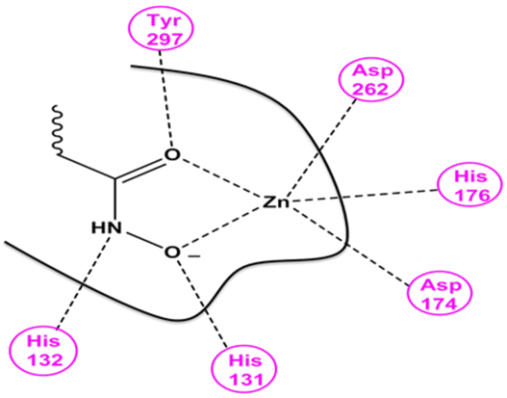


Figure 3: Chelation of hydroxamic acid group with zinc ion in the active site of HDLP.

A large number of hydroxamic acid containing HDACIs are known. Among the first known hydroxamates was the natural HDACI trichostatin A (TSA) **(Figure 4)**. [88] TSA was the first HDACI identified and belonging to the hydroxamate group. It is an organic antibiotic produced by *Streptomyces hygroscopicus* and further studies proved that it has potent HDAC inhibitory activity [88,89] but not entered clinical use due to its toxicity. [90]

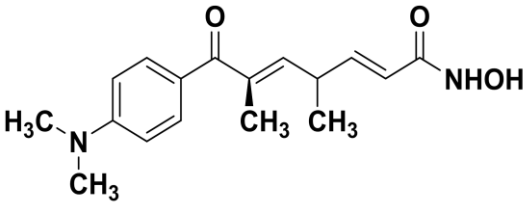
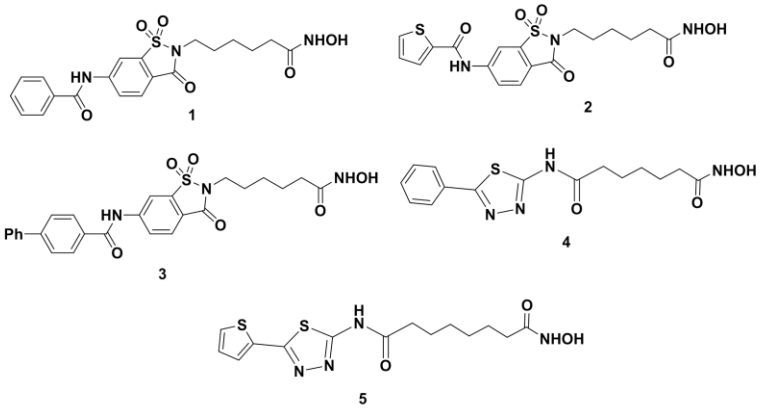


Figure 4: Structure of TSA.

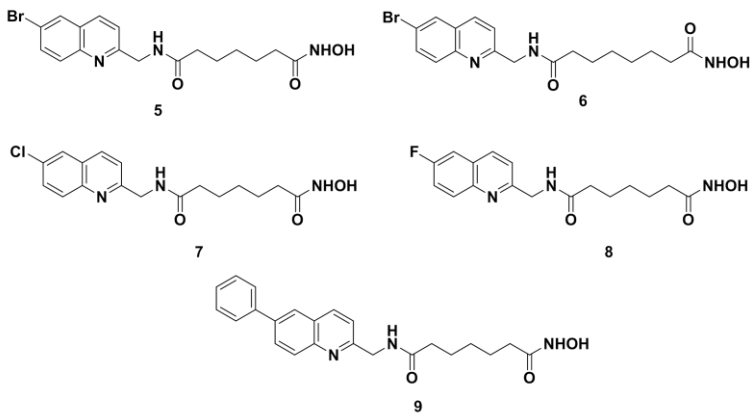
Moreover, SAHA, belinostat, and panobinostat are another hydroxamate HDACIs that approved by the FDA for treatment of CTCL, PTCL and MM. Due to the importance of hydroxamic acid derivatives as promising anticancer agents that are effective against different cancer types, several research groups have been interested in the development of newer more potent and less toxic agents.

A series of saccharin hydroxamic acids [91] and 1,3,4-thiadiazole-containing HDACIs [92] have been developed. Among them, compounds **1-5** showed similar or better HDACs inhibitory activity compared with SAHA. Compound **2** specifically exhibited potent antiproliferative activity against breast cancer cell MDA-MB-231 and prostate cancer cell PC-3

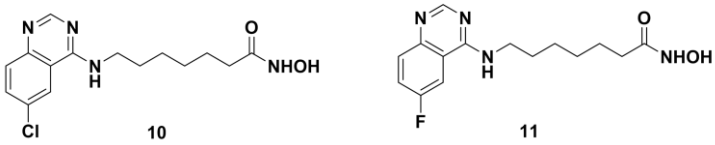
with IC_{50} 4.34 μM and 9.28 μM, respectively. A linker with five carbon units between the ZBG and the saccharin ring as a cap group was optimal for potency. In order to improve the potency of compound **4,** the phenyl moiety is replaced by its bioisostere thienyl moiety. The formed thienyl derivative **5** showed higher activity than SAHA with IC_{50} of 310 nM and 416 nM, respectively where the 6-carbon linker afforded the most potent cell growth inhibition.



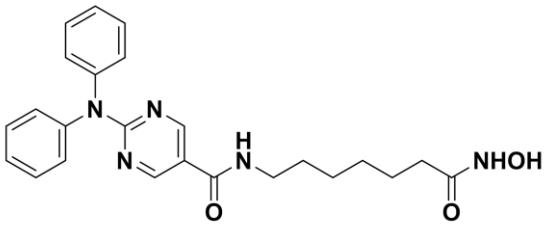
Wang *et al*., have reported the synthesis of a series of quinoline HDACIs **5-9**. **[**93] The prepared compounds showed good inhibitory activities against HDACs and potent antiproliferative activities against some tumor cell lines. Compound **5** exhibited better HDAC inhibitory activity than SAHA with IC_{50} value of 85 nM and 161 nM, respectively. Moreover, compound **5** showed better antiproliferative activity than SAHA. The substituents on the C4 and C6-position of the quinoline ring significantly affected activity. Substituents on the C4-position of quinoline ring decreased the enzyme inhibitory activity. Meanwhile, substituents on C6-position of quinoline ring enhanced the enzyme inhibitory activity; it is considered crucial for binding affinities. The best substituent in this position was halogens and by replacing halogen with a phenyl group resulted in a decrease of enzymatic inhibitory activity. Regarding the linker length, the most suitable length was 5 that helped the ZBG to chelates the zinc ion.



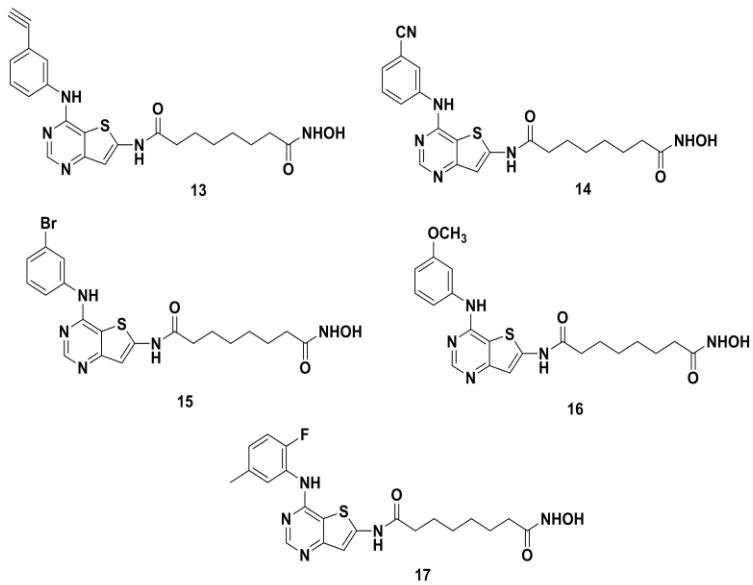
Zhang *et al*., have reported the synthesis of a series of hydroxamic acid-based HDACIs with 4-aminoquinazolinyl moieties as cap groups **10, 11**. **[**94**]** These compounds showed more potent HDACs inhibition activity than SAHA. In addition, they selectively inhibited HDAC1, 2 over HDAC8, and not possessing significant toxicity to human cells. The IC_{50} values are 3.08 ± 0.19 nM for compound and 8.17 ± 1.15 nM for 6-F derivative. Introduction of 6-Cl can increase potency than the corresponding 6-F with 10-fold activity than SAHA.



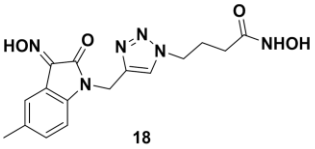
Drug development in hydroxamic acid HDACIs resulted in the introduction of Ricolinostat (ACY-1215) [95] **12**, a potent selective HDAC6 inhibitor, it inhibited the HDAC6 with IC_{50} of 4.7 nM. This compound is currently under phase II clinical trials. It is effective alone or in combination with dexamethasone and either bortezomib or lenalidomide which gave a synergistic effect against multiple myeloma.



Recently thienopyrimidine based HDACIs **13-17** have been synthesized and evaluated for their antiproliferative and HDAC inhibitory activity on leukemia cancer cell RMPI-8226 and colon cancer cell HCT 116. [96] These derivatives showed good activities against HDAC1, 2, 3. In particular, the thienopyrimidine derivative **13** exhibited excellent inhibitory activity against HDAC1, HDAC3, and HDAC6 with IC_{50} values 29.81 ± 0.52 nM, 24.71 ± 1.16 nM, and 21.29 ± 0.32 nM, respectively. It showed strong antiproliferative activity against these two cancer cell lines with IC_{50} of 0.97 ± 0.072 μM and 1.01 ± 0.033 μM, respectively.



A novel hydroxamic acids have been designed by Dung et al., that include 2-oxoindoline as a cap group. [97] These hydroxamic acids **18, 19** potently inhibited a class-I HDAC2 isoform with IC_{50} values 1.28 μM for 5-CH_3 and 0.91 for 5-OCH_3. They exhibited cytotoxicity up to 8-fold more potent than SAHA in three human cancer cell lines, including the colon cancer SW620, prostate cancer PC3 and pancreatic cancer AsPC-1. In designing these compounds, they incorporated the triazole moiety to increase hydrogen bonding with the amino acid in the active binding sites of HDAC, and still serving as a part of a linker between the 2-oxoindoline and hydroxamic acid moieties.



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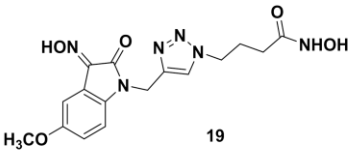

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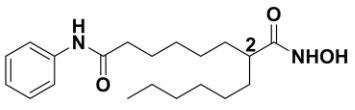
Moreover, different SAHA analogs have been synthesized to improve selectivity. The nonselective HDACI SAHA was modified at the C2, C3, C4, C5, and C6 positions of the linker introducing compounds **20-24**. [98–102] The C2-n-hexyl SAHA analog **20** displayed 49-300 fold selectivity for HDAC6 and 8 over HDAC1, 2, and 3. Substituents on the C3 position **21** displayed HDAC6 selectivity, compared to the broad-spectrum inhibitor SAHA and showing IC_{50} of 350 nM, which is only four-fold less potent than SAHA. The potency of analogs decreased by increasing the size of C_3 substituent and the methyl substituent displayed the most potent analog. The C4-benzyl SAHA analog **22** exhibited dual HDAC6/8 selectivity with 520 to 1300 fold increase for HDAC6 and HDAC8 over HDAC1, 2, and 3, and IC_{50} values of 48 and 27 nM with HDAC6 and 8, respectively. Longer substituents at the C4 position led to greater HDAC6/8 selectivity. Moreover, C5-modified SAHA analog **23** also exhibited dual selectivity to HDAC6 and HDAC8 over HDAC1, 2, and 3, with only a modest reduction in potency in HDAC6 inhibition but enhanced HDAC 8 inhibition compared to SAHA. It showed 8-21 fold increase in selectivity for HDAC6 and HDAC8 over HDAC1, 2, and 3 with IC_{50} values of 270 and 380 nM for HDAC6 and HDAC8, respectively. The size of the substituent has affected selectivity, bulky substituents in the linker region enhanced HDAC6/8 selectivity due to the wider active site entrance of both HDAC6 and HDAC8 compared to HDAC1, 2 and 3 that exhibited steric clash with the compound entered and leading to a reduction in inhibition of HDAC1, 2, and 3. Furthermore, C6-SAHA analogs have been synthesized and the selectivity and potency were measured. C6-phenyl SAHA **24** analogue was the most potent analog, displaying IC_{50} values in nanomolar concentrations. It experienced four-fold reduced potency compared to SAHA. In addition, it inhibited HDAC1, HDAC3, and HDAC6. On contrast, the C6-methyl SAHA analog showed modest selectivity for HDAC1 and HDAC3 over HDAC6 at 500 nM. The aforementioned results revealed that small structural changes in the linker region of SAHA could significantly impart selectivity.



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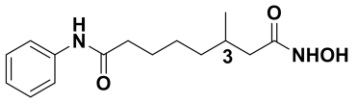

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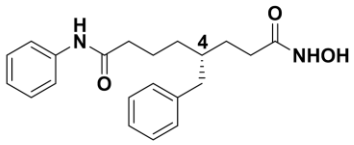

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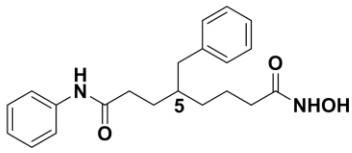

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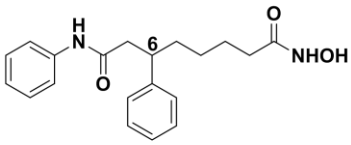

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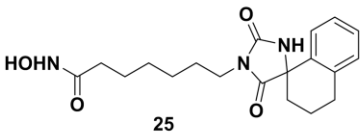
Aboeldahab *et al*., have designed a new HDACIs that involved spirohydantoin and 1,2,4 triazole groups **25-27**. [103] Compound **25** was the most potent growth inhibitor against breast cancer cell line MCF-7, having IC_{50} of 2.56 μM. Conversely, it showed low activity against hepatic cancer cell line HepG2. In addition, the six carbon linker gave the highest HDAC inhibitory activity with IC_{50} value comparable to SAHA against HDAC4 and low selectivity at HDAC1. Moreover, increasing the linker length increased the HDAC inhibitory activity. In addition, compounds **26** and **27** showed significant HDAC inhibitory activities against the four tested HDAC isoforms. Compound **26** exhibited potent antiproliferative activity against MCF-7 cell line but compound **27** exhibited potent antiproliferative activity against HepG2 cell line. Moreover, compound **27** experienced a potent inhibition of TUBb polymerization and, showed higher potency than CA4.



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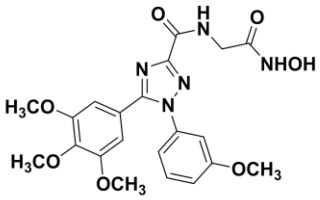

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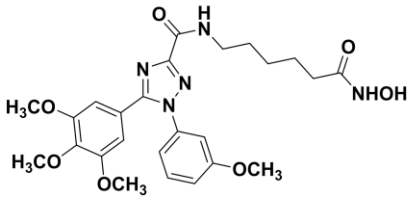

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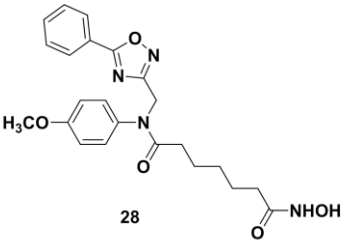
Another series of 1,2,4-oxadiazole containing HDACIs have been developed. [104] Compounds **28** and **29** induced apoptosis in HepG2 cells higher than SAHA with IC_{50} of 1.07 μM, 1.03 μM and 4.50 μM, respectively. Moreover, they potently inhibit HDAC1 enzyme with IC_{50} of 8.2 nM and 10.5 nM, respectively.



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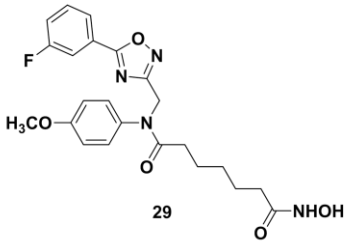

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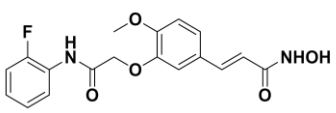
The *N*-hydroxyacrylamide moiety is considered a promising linker in the design of newer HDACIs. This linker has occurred in the two important FDA approved HDACIs belinostat and panobinostat where the cinnamide moiety is considered as the hydrophobic spacer. [105]

A series of HDACIs that involved isoferulic acid derivatives have been synthesized to improve the affinity and activity of the ferulic acid-based HDACIs that was previously synthesized. [106,107] The two compounds **30** and **31** displayed a good HDAC inhibitory activity with IC_{50} values of 0.73 ± 0.08 and 0.57 ± 0.16 μM, respectively. Compound **30** exhibited moderate antiproliferative activity with an IC_{50} value of 3.91 ± 0.97 μM against HeLa cells.



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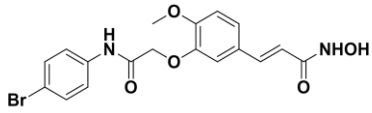

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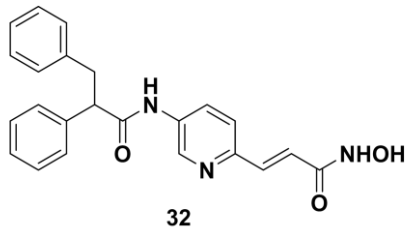
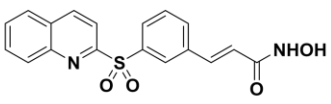
Pompo *et al*., designed a new HDACI **32** having a cinnamoyl moiety. This compound showed potent cytotoxicity, which induced apoptosis and arrest development in osteosarcoma cancer stem cells at lower concentrations (0.1 μM). [108] It is considered a pan-HDACI, efficient in inhibiting all the HDAC isoforms 1-11 in the range 0.08-12 μM.



32

Moreover, a series of novel *N*-hydroxyacrylamides have been synthesized **33** and **34**. [109] The presence of *N*-hydroxyacrylamide moiety was associated with significant HDAC inhibitory activity. Compound **30** and **31** showed more potency than FDA approved analogs belinostat and SAHA at HDAC1, 2, 6 and 8 but didn't show any HDAC isoenzyme selectivity. The SAR showed that the presence of *N*-hydroxyacrylamide group at C3 position experienced the most potent antiproliferative activity, shifting of this moiety from C3 to C4 led to a mild decrease of cellular activity. In addition, bioisosteric replacement of SO2 with CO led to a slight decrease in antiproliferative activity. Moreover, replacement of the quinoline ring with a pyridine led to a decrease in cellular activity.



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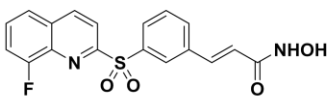
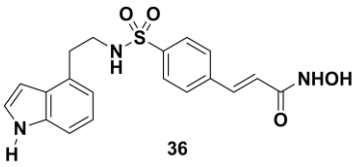
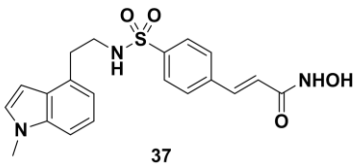


34

In addition, a series of HDACIs involving 4,5-indolyl-N-hydroxyphenylacrylamides has been synthesized and evaluated for their antiproliferative and HDAC inhibitory activity. [110] The research study revealed that 4-Indolyl compounds **36** and **37** have potent inhibitory activity against HDAC1 (IC_{50} 1.28 nM and 1.34 nM, respectively) and HDAC 2 (IC_{50} 0.90 and 0.53 nM, respectively). The study also showed that *para*-substitution for N-hydroxyphenylacrylamides moiety was the best position for optimal activity.

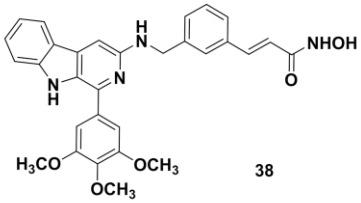


36



37

Recently, Ling *et al*., have prepared a series of novel hybrids of β–carboline and N-hydroxycinnamamide as HDACIs to overcome drug-resistant hepatocellular carcinoma. [111] Compound **38** showed strong antiproliferative activity with IC_{50} values of 1.01 μM, 0.41 μM, 0.87 μM, 0.69 μM human cancer cells SUMM-7721, Hep G2, HCT116, H1299, respectively. In addition, it selectively inhibited HDAC1/6 with IC_{50} of 1.3 μM, 3.1 μM, respectively. This selectivity of **38** for HDAC1/6 may attributed to its active fragment N-hydroxycinnamamide, which form bi-chelation with the zinc ion in the active site through its hydroxamic acid group, also be able to form sandwich-like π–π interactions with two parallel phenylalanine residues of HDAC1/6 by its vinyl benzene group. Moreover, it showed high anticancer activity against drug-sensitive HepG2 and Bel7402 cells and drug-resistant Bel7402/5FU cells. Also, compound **39** exhibited high HDAC1 inhibitory activity but still lower than **38** with IC_{50} of 2.8 μM.



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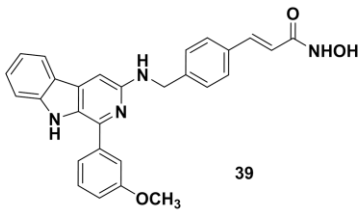
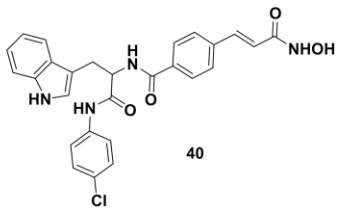


39

Furthermore, a series of novel and potent *N*-hydroxycinnamamide-based HDACIs that involved indole as a cap group have been designed **40**-**44**. [112] All of these compounds exhibited selectivity on HDAC1 with compound **43** being the most one with IC_{50} of 0.92 μM. They also showed potent antiproliferative activity against five cancer cell lines.



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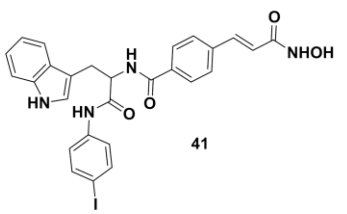

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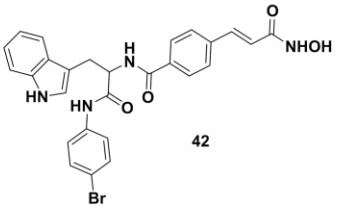

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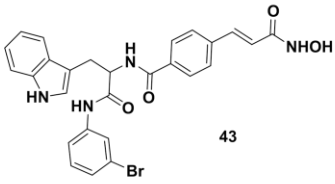

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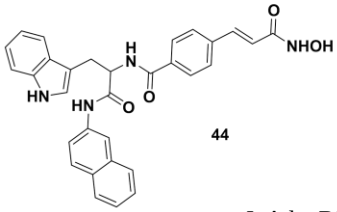
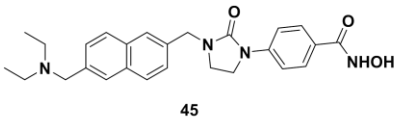


44

On the other hand, HDACIs with phenylimidazolidin-2-one as a new linker was introduced **45-48**. [113] In particular, Compound **45** displayed a potent HDAC1 inhibitory activity with IC_{50} of 2.7 nM. In addition, it showed 6-9 fold increase in activity compared to vorinostat, with GI_{50} value of 0.1, 0.086, 0.11 µM against prostate cancer cell PC-3, leukemia cancer cell HL-60 and colon cancer cell HCT-116, respectively. The other compounds **46-48** in this series also exhibited potent HDAC1 inhibitory activity but lower than **45** with IC_{50} of 5.4, 5.4, and 4 nM, respectively.



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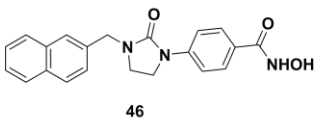

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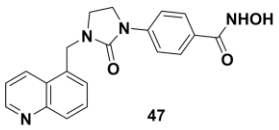

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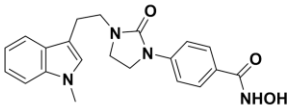
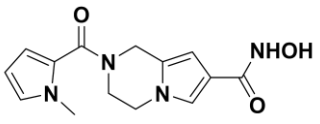


48

Blackburn *et al*., have prepared series of 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine hydroxamic acid derivatives **49** and **50**. [114] The pyrrole moiety serves as a cap group that imparts potency and selectivity to the compounds than larger groups like indole. Compound **49** showed a potent HDAC6 inhibitory activity with IC_{50} of 33 nM. This represents 200-fold selectivity versus nuclear extract (HDAC1, 2) and 100-fold selectivity versus HDAC8.



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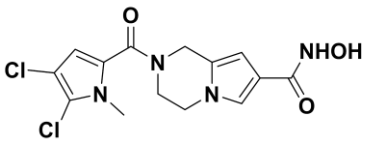
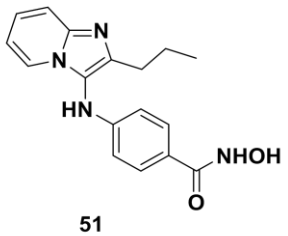


50

Moreover, Mackwitz *et al*., have synthesized a series of HDACIs with imidazo[1,2-a]pyridine based cap groups **51-53**. [115] Compound **51** having 4-aminophenyl linker is a selective HDAC6 inhibitor, it selectively inhibited HDAC6 with IC_{50} 0.058 µM and selectivity factor 38. Compounds **52** and **53** also potently inhibit HDAC 6 with IC_{50} 0.05 and 0.076 µM, respectively but with lower selectivity factor (3 and 11, respectively).



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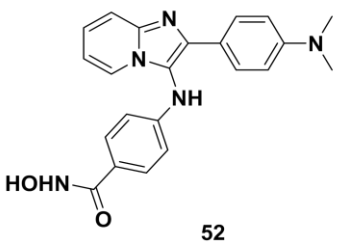

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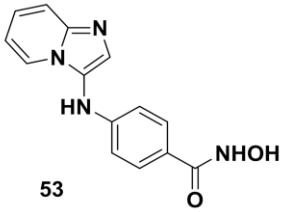
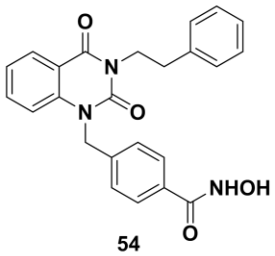


53

Moreover, a series of quinazoline 2,4-dione based hydroxamic acids **54-56** experienced a selectivity inhibition toward HDAC6. [116] Compound **54** experienced the most potent with selective inhibition of HDAC6 with IC_{50} 4 nM. IC_{50} of compounds **55** and **56** were 5 and 20 nM, respectively. From the SAR studies, replacement of the phenyl ring with other equivalent rings or changing the position of the hydroxamic acid group reduced the HDAC6 inhibitory activity.



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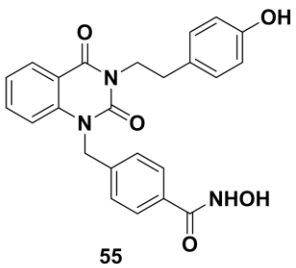

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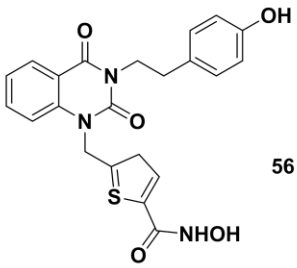
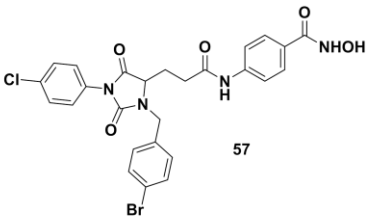


56

A series of 2,4-imidazolinedione derivatives as novel HDAC6 selective inhibitors have been designed **57-59**. [117] They exhibited good HDAC6 inhibitory activity with IC_{50} of 9.7, 4.4, and 7.6 nM, respectively. In addition, they showed potent antiprolifertative activity against five cancer cell lines with IC_{50} in the range of 0.23 to 9.45 nM. Compound **58** induced apoptosis in HL-60 cell line by activating caspase 3.



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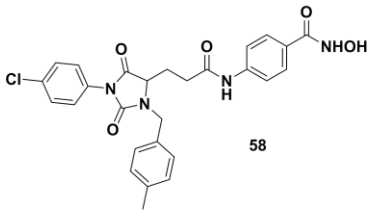

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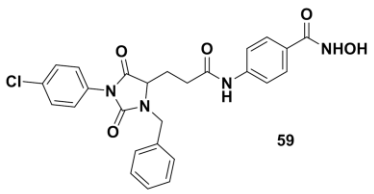


59

Benzamides or ortho-Aminoanilides

The benzamide HDACIs were the second class of HDACIs that exhibited a good anticancer activity and bound the zinc ion in the HDAC active site through the benzamide moiety. [118,119] They exert more selectivity to specific HDAC isoforms than the hydroxamate class. Several examples of benzamide inhibitors are in clinical studies such as Entinostat (MS-275, phase III), Mocetinostat (MGCD0103, phase II), tacedinaline (CI994, phase II) (**Figure 5**). [120–124]

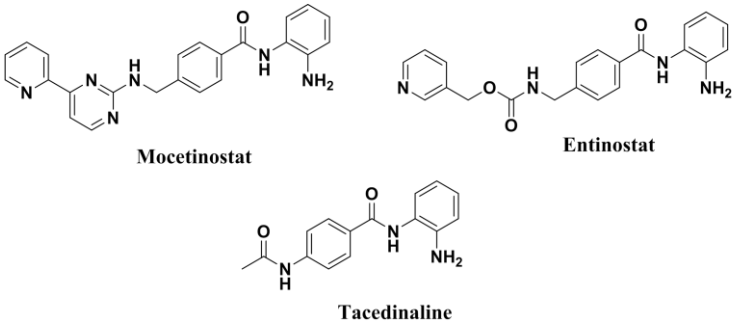
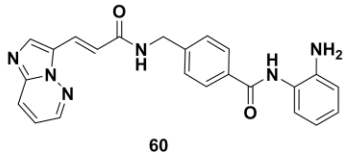


Figure 5: Structure of entinostat, mocetinostat and tacedinaline benzamides.

A series of HDACIs bearing a bicyclic heterocycle moiety **60-62** have been designed and synthesized based on the lead compound MS-275. [125] They exerted a reasonable inhibitory potency against HDAC1 with IC_{50} of 0.118 μM, 0.129 μM and 0.120 μM, respectively that was higher than that of MS-275 (IC_{50}= 0.273 μM). They also exhibited more potent antiproliferative activities than MS-275. From the SAR studies, the introduction of fluoro group at the benzamide ring lower antitumor activities against three cancer cell lines. The inhibitory activities of bicyclic heterocyclic substituted compounds were better than pyridinyl substituted compounds. When replacing the methyl with ethyl results in reduction of the inhibitory activity.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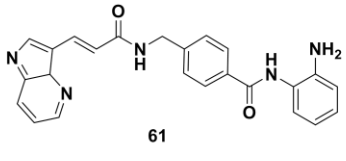
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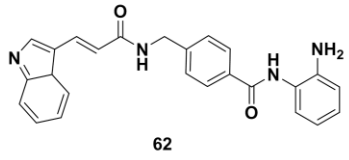
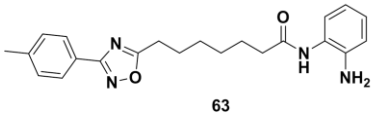

62

Cai *et al*., have synthesized a series of HDACIs that involved 2-aminobenzamide moiety **63** and **64**. [126] Compound **60** achieved a significant antiproliferative activity with IC_{50} values of 0.41 and 0.46 μM toward NCI-H661 and U937, respectively, which somewhat better than that of Vorinostat. Moreover, Compound **63** exhibited a higher selectivity for HDAC1 over HDAC2 with IC_{50} value of 140 nM toward HDAC1, and 680 nM toward HDAC2. Compound **64** showed good antiproliferative activity with IC_{50} values of 0.69 and 0.73 μM toward NCI-H661 and U937, respectively. Also, it exerted higher HDAC1 inhibitory activity with IC_{50} of 210 nM.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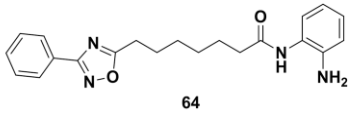
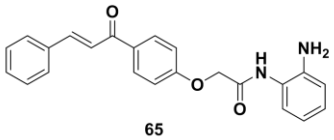

64

Mohamed *et al*., have synthesized a group of novel chalcone derivatives that comprising 2-aminobenzamide group as ZBG. [127] The prepared compounds **65** and **66** showed a significant HDAC inhibitory activity. Compound **65** showed weak anticancer activity against three cancer cells lines HCT-116, MCF-7, and HepG2 with IC_{50} > 100 μM. However, compound **66** exhibited comparable antiproliferative activity with IC_{50} 3.02-12.99 μM as SAHA as a reference drug.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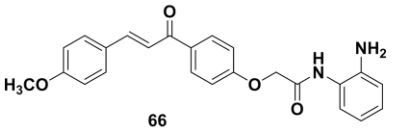
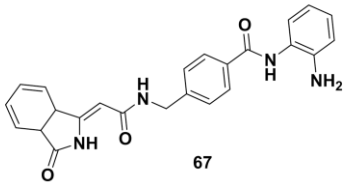

66

Chen *et al*., have developed a series of novel isoindolinone based HDACIs [128]. Compounds **67** and **68** experienced inhibitory activities against HL-60 and K562 cell lines with IC_{50} values ranging from 193 to 450 nM. Moreover, they exhibited better HDAC1 inhibitory activity than chidamide with IC_{50} values of 65.6 nM, 65.1 nM, and 296 nM, respectively. The SAR study showed that replacement of F in compound **68** with chlorine or methyl substituents decreased the HDAC1 inhibitory activity which might be resulting from hindrance at this position.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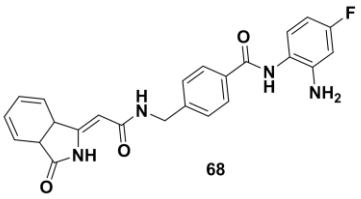
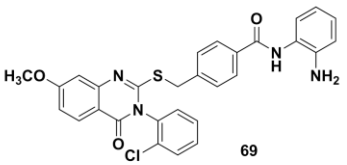

68

A series of novel 2-aminobenzamide derivatives with thioquinazolinone have been synthesized as HDACIs **69-72**. [129] They exhibited higher antiproliferative activities towards three cancer cell lines: A375, A549 and SMMC7721 compared to CS055, MS-275, and CI994. Compounds **69-72** showed excellent inhibitory activity against HDAC1 with IC_{50} of 0.38 μM, 0.29 μM and 0.01 μM, and 0.1 μM respectively. They also showed HDAC2 inhibition with IC_{50} of 0.61 μM, 0.53 μM and 0.16 μM and 0.18 μM, respectively. Compound **71** exhibited higher antiproliferative activities against three cancer cell lines with IC_{50} of 0.98 μM, 0.75 μM, and 0.03 μM, respectively.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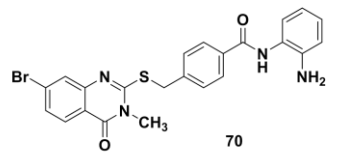
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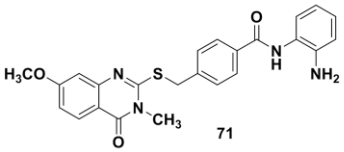
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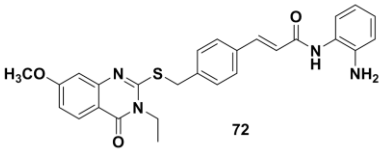
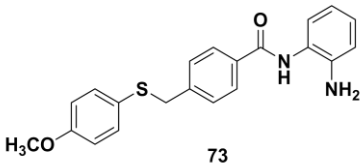

72

In addition, Yun *et al*., have synthesized a series of thioether-based 2-aminobenzamide HDACIs. [130] Compounds **73** and **74** showed potent antiproliferative activities against five cancer cell lines with IC_{50} in the range of 1.64-3.80 μM. Moreover,

they showed potent HDAC inhibitory activity against HDAC1 and 2 With IC_{50} of 0.016 μM and 0.205 μM for **73** and 0.071 μM and 0.144 μM for **74**, respectively.



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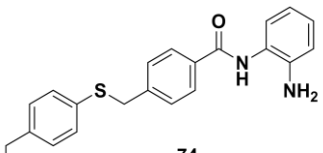
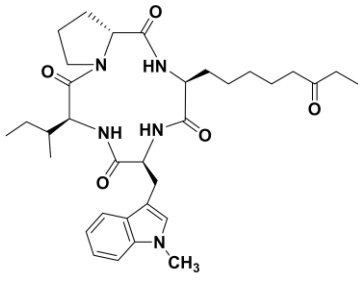


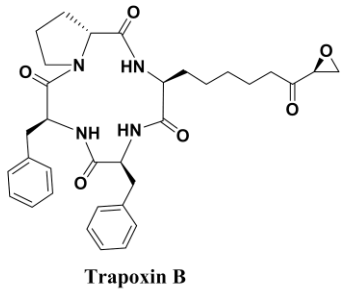
74

Cyclic peptides

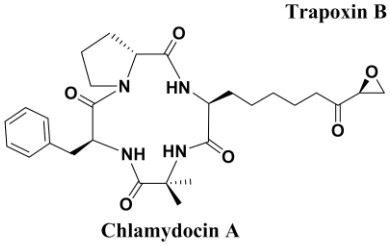
Cyclic-peptide HDACIs are the most complex class of all HDACIs such as apicidin, romidepsin (FK228), trapoxin B and chlamydocin **(Figure 6)**. [131–133] The natural product romidepsin (FK-228) which has been isolated from *Chromobacterium violaceum* is the prototype of this class. Romidepsin is a prodrug that reduced to the active form (RedFK) after uptake into the cells **(Figure 7)**. [134–136] This naturally occurring compound exhibit very strong HDAC inhibitory activity than hydroxamate and other HDACIs, even though its thiol ZBG is a weaker group. [137]



Apicidin

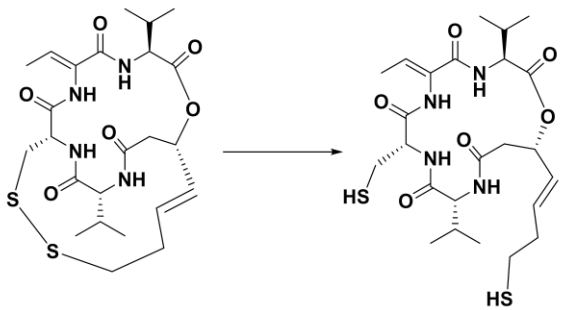


Trapoxin B



Chlamydocin A

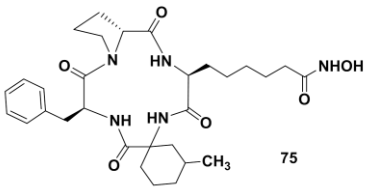
Figure 6: The structure of Apicidin, Trapoxin B, Chlamydocin A



Romidepsin (FK228) RedFK

Figure 7: The structure of Romidepsin (FK228) and its activated form (RedFK).

Based on the structure of natural and synthetic compounds such as TSA, SAHA, chlamydocin, and FK228, numerous HDACIs have been developed as potential anticancer agents. Wang *et al*., have synthesized a series of chlamydocin analogs **75** and **76** that have combined with various ZBGs. Compound **75** exhibited better antiproliferative effects than TSA against breast cancer cell MCF-7 with an IC_{50} value of 26 nM. Moreover, compound **75** was an effective inhibitor of HDAC1 and HDAC4 with IC_{50} of 15 nM and 14 nM, respectively. This hybrid of cyclic peptide class and hydroxamate class termed cyclic hydroxamic acid peptide. On the other hand, compound **76** also showed good inhibition of HDAC1 and HDAC4 with IC_{50} of 14 nM and 19 nM, respectively. [138]



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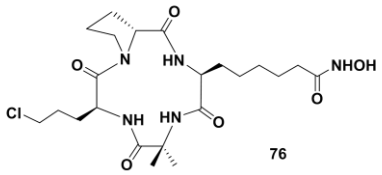
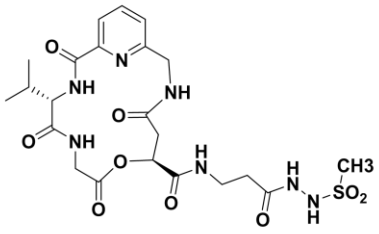


76

New cyclodepsipeptide analogs **77** and **78** have been synthesized and evaluated for its inhibitory potency and selectivity towards HDAC1, HDAC3 and HDAC6 isoenzymes. They showed potent HDAC3 inhibitory activity with IC_{50} of 10.9 μM and 1.4 μM, respectively. Sulfonylhydrazide group serves as ZBG and the two oxygen atoms of sulfonyl group chelates with the zinc ion. [139**]**



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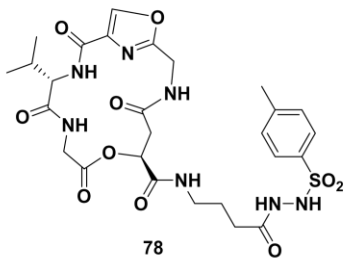
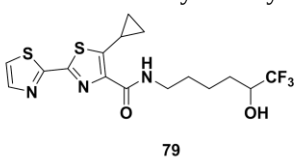


78

Electrophilic ketones

Electrophilic ketones have been used as a ZBG replacement and included trifluoromethyl ketones. They showed potent HDAC inhibitory activity. [140] This moiety is readily hydrated in aqueous media and binds to the zinc ion in the active site of HDAC enzyme. [141]

Gong *et al*., have synthesized a series of bisthiazole-based compounds with a trifluoromethyl ketone as the ZBG **79-81**. [142] In particular, compound **81** exhibited excellent inhibitory activity against human HDAC1, 3, 4 and 6, with an IC50 of 20-30 nM. In addition, it showed improved antiproliferative activity against cancer cell lines RPMI 8226, NCI-H929 with IC50 of 0.08 and 1.23 μM, respectively. The reduction of the ketone group in compound **81** reduced the HDAC inhibitory activity as in compound **79**. In addition, changing the length of the linker or cyclopropyl group to isobutyl or benzyl reduce the HDAC inhibitory activity of compound **81**.



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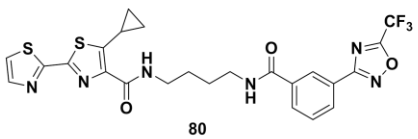

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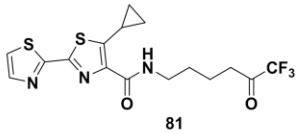
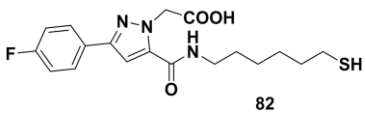


81

Miscellaneous

There are several HDACIs that include different ZBGs and the most common of them were thiol based HDACIs. Thiols are well-known chelators of zinc-dependent enzymes. Replacement of the hydroxamate group of SAHA with a thiol group produced thiol-based SAHA that has found to be as potent as SAHA with IC_{50} of 0.21 µM. [143]

A series of novel thiol-based HDACIs included 3-phenyl-1H-pyrazole-5-carboxamide scaffold as a cap group was synthesized. [144] Compound **83** showed a potent HDAC inhibitory activity with IC_{50} of 0.08 µM. Moreover, it exhibited more selectivity at HDAC6 than HDAC1 with IC_{50} of 0.09 µM and 0.13 µM, respectively due to incorporation of aliphatic carboxylic acid at position 1 in pyrazole ring. Compound **82** was more selective HDAC6 than compound **83** with IC_{50} of 0.04 µM. Alkyl chain length with 4 carbon atom at N-1 of pyrazole ring was optimal for HDAC inhibitory activity, better than 2 or 3 carbon as in compound **83** that has high inhibitory activity. Addition of methyl group on pyrazole C-4 position diminished the HDAC inhibition activity. Replacement of thiol group with mercaptoacetamides or mercaptopropanamides decreases the inhibitory activity.



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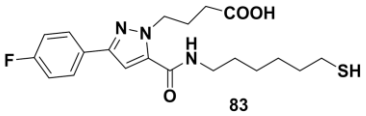

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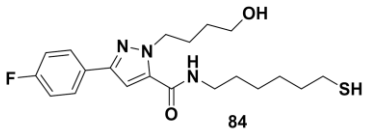
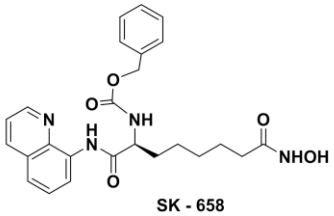
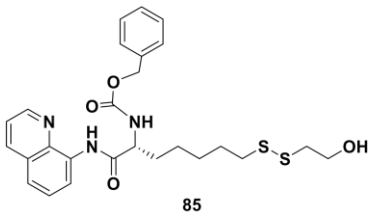


84

Islam *et al*., have prepared a disulphide SK-658 analogs **85** and **86** that exhibited a higher HDAC inhibitory activity than SAHA and SK-658 against HDAC1, 4 and 6 with IC_{50} in the range of 2 to 8.2 nM. [145] The disulphide group reduced to the sulfhydryl group by dithiothreitol (DTT) that has a strong affinity to the active site.



SK - 658



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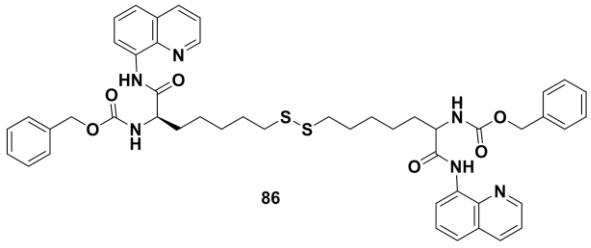

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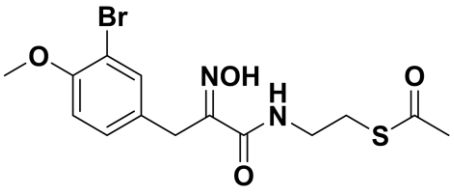
In addition, thioesters derived from the natural compound psammaplin A displayed moderate to high potency in cytotoxic and HDAC inhibitory activity. Thioester compound **87** exhibited potent inhibitory activity against recombinant HDAC1 with IC_{50} value of 5 nM. It also had potent cytotoxic activity against breast cancer cell MCF7 with IC_{50} of 3.2 µM. [146]



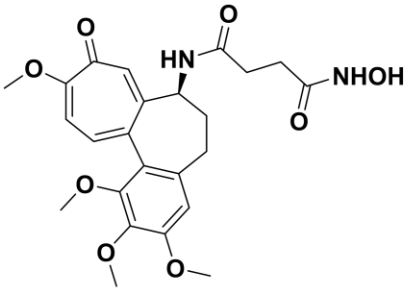
87

3. Multi-targeted HDACIs

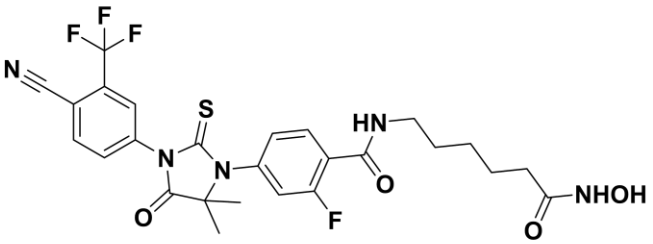
The cancer disease depends on more than one receptor or signaling pathway for its initiation and progression as a result the drugs that target one receptor may be inadequate treatment. To overcome this obstacle problem, multi-targeted therapeutics have been developed that was one of the most effective strategies and advantageous than mono-therapies. This combination therapy gave a synergistic or potentiation effect that led to significant anticancer activity. [147] A multi-targeted drug is an agent that including two or more different pharmacophores integrated into the same structure to yield a hybrid molecule. Hybrid molecules with HDAC inhibitory activity and an additional activity has become an attractive area of the research field and are under development [148]. Several examples in these therapies include HDACIs with topoisomerase inhibitors, antiestrogens, antiandrogens, LSD inhibitors, tubulin inhibitors, VEGFR-2 inhibitors, EGFR/HER2 kinase inhibitors, JAK-2 inhibitors, Bcl-2 inhibitors, $BRaf^{V600E}$ inhibitors, and DNMT inhibitors **88-100**. [149–161]

4. Conclusion and future prospectives of HDACIs

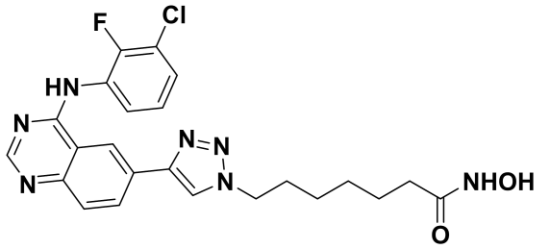
HDACIs have emerged, in the last years, as potent agents in the treatment of cancer. HDAC inhibitors interfere with HDAC activity and result in cell cycle arrest, differentiation and apoptosis in cancer cells. As a result, HDAC inhibitor-based therapies have gained much attention for cancer treatment. There are several HDACIs in market (vorinostat, romidepsin, belinostat, and panobinostat, pracinostat and chidamide) and others in clinical trials that displaying significant activity in both hematological and solid tumors of various tissues. HDACIs not only play a role in the etiology of cancer but also in the etiology of various clinical disorders such as central nervous diseases, systemic sclerosis, cardiovascular diseases, chronic pain and depression. [162–167] Thus, identification of new multi-target HDACIs to overcome cancer resistance, the development of selective HDACIs and the optimization of HDACIs in combination chemotherapy continue to attract more and more attention to their development by researchers. The search for more selective HDAC isotypes may overcome the toxicity associated with the treatment with HDACIs. In this review, we focused on the recent developments in HDACIs, the multi-targeted agents and the effect of HDACIs on cancer cells.



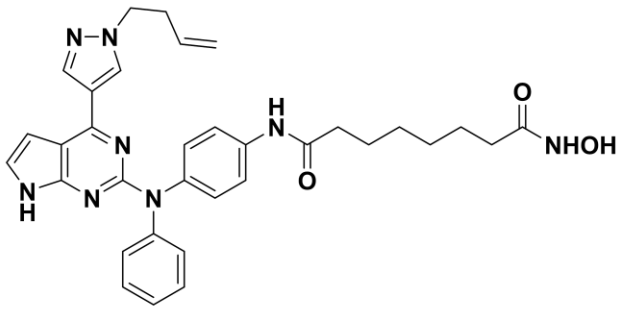
88: HDACI + Tubulin inhibitor
HDAC1 IC_{50}=0.72 μM
HDAC3 IC_{50}=0.44 μM



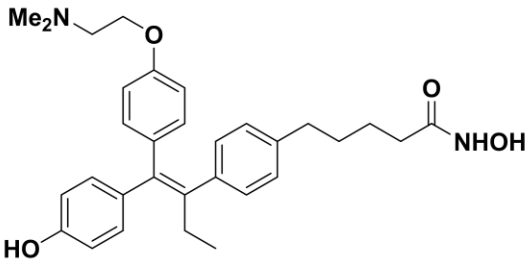
89: HDACI + Antiandrogen
HDAC6 IC_{50}=0.0356 μM
AR binding IC_{50} = <0.03 μM



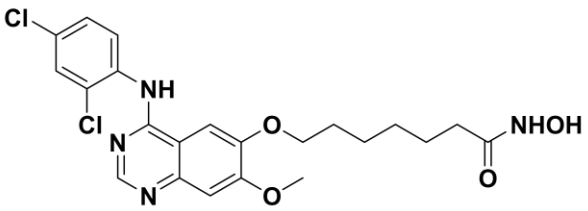
90: HDACI + EGFR/HER2 Inhibitor
HDAC1 IC_{50}=0.12 nM
HDAC6 IC_{50}=0.72 nM
EGFR IC_{50}=3.2 nM



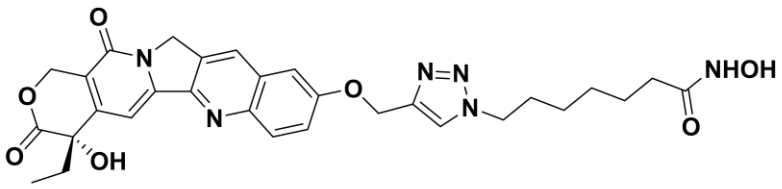
91: HDACI + JAK2 Inhibitor
HDAC1 IC_{50}=83 nM
HDAC6IC_{50}=0.25 nM
JAK2 IC_{50}=0.041 nM



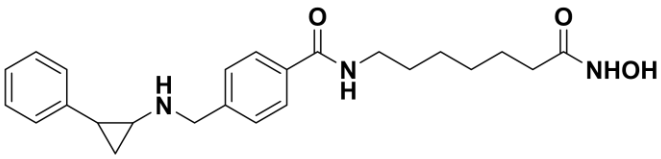
92: HDACI + Antiestrogen
HDAC3 IC_{50}=0.73 μM
HDAC6 IC_{50}=0.30 μM



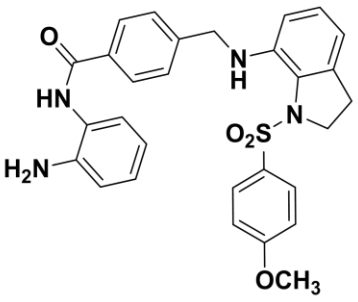
93: HDACI + VEGFR-2 Inhibitor
VEGFR-2 IC_{50} = 84 nM
HDAC IC_{50} = 2.8 nM



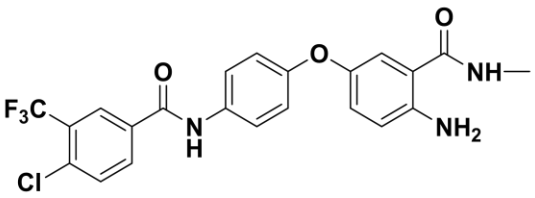
94: HDACI + Topoisomerase I Inhibitor
HDAC1 IC_{50}=37 nM
HDAC6 IC_{50}=81 nM
HDAC8 IC_{50}=1046 nM



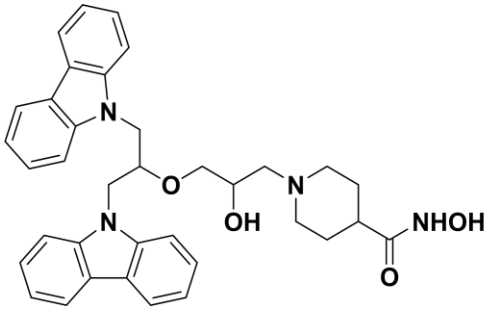
95: HDACI + LSD1 Inhibitor
HDAC1 IC_{50}=15 nM
HDAC2 IC_{50}=23 nM
LSD1 IC_{50}=1.20 μM



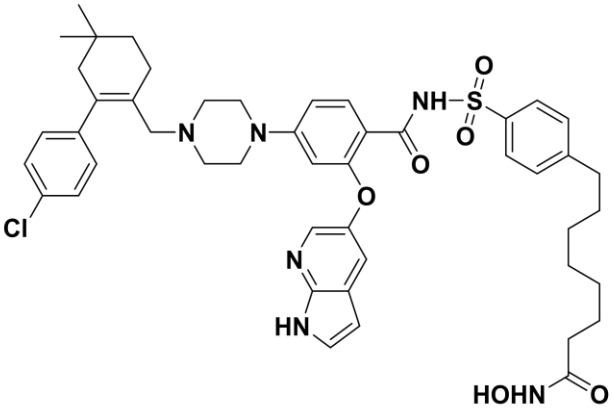
96: HDACI + tubulin inhibitor
Tubulin inhibition IC_{50}=1.1 μM
HDAC1 IC_{50}=0.221 μM



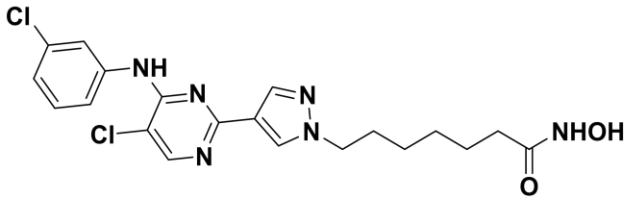
97: HDACI + $BRaf^{V600E}$ inhibitor
HDAC 1 IC_{50}=1.17 μM
$BRaf^{V600E}$ IC_{50}=0.073 μM



98: HDACI + DNMT1 inhibitor
DNMT 1IC_{50}=2.05 μM
HDAC 1IC_{50}=4.16 μM



99: HDACI + Bcl-2 inhibitor
Bcl-2 IC_{50}=0.25 μM
HDAC 6 IC_{50}=19 nM



100: HDACI + JAK1 inhibitor
JAK2 IC_{50}=0.01 μM
HDAC IC_{50}=0.02 μM

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