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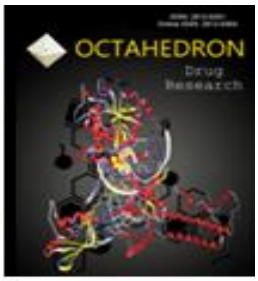

Recent review on selective histone deacetylase inhibitors in cancer therapy

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ABSTRACT

Cancer is the most serious disease afflicting humans and a primary cause of death on a global scale. Chemotherapy continues to be one of the most essential cancer treatments, in addition to surgery and radiotherapy. Recently, the use of targeted anticancer medications as an approach for optimizing antitumor therapy has been advocated. One of the most well-established cancer targets is histone deacetylases (HDACs). HDAC inhibitors (HDACis) have evolved as one of the most effective anticancer medications due to their capacity to destroy cancer cells aggressively via alteration of the chromatin structure or inhibition of their activity. The discovery of selective HDACs has recently garnered considerable interest for their diverse biological activities and potential therapeutic agents with fewer adverse effects than approved pan inhibitors. This review provides an overview of isoform- and class-selective HDAC inhibitors, including the IC50 values and biological effects on various types of cancer.

1. Introduction

Histone deacetylases (HDACs) are NAD^+ or Zn^{2+}-dependent enzymes in procaryotes and eucaryotes that regulate the cellular proteins' acetylation condition. Eighteen mammalian HDACs are categorized into four classes based on their similarity to yeast deacetylases and their discovery time: class I compromises of HDAC1, 2, 3 & 8. Class II is further subdivided into IIa, which involves HDAC4, 5, 7, 9, and IIb, which involves HDAC6, 10, and class IV has just HDAC11, which has structural similarities to classes I and II [1, 2]. In class III SIRT1-7, NAD^+ is used as a cofactor, whereas in classes I, II, and IV, Zn^{2+} is used as a cofactor [3, 4].

HDACs are crucial epigenetic enzymes that regulate different elements of life, such as protein activities and gene expression. It is essential to highlight that increased HDAC expression was detected in several cancer types [5].

For example, pancreatic and colorectal malignancies are related to transcriptional HDAC1 overexpression. In addition, both colon and lung cancer exhibited HDAC3 overexpression, whereas HDAC8 was shown to be overexpressed in neuroblastoma [6, 7]. HDACs can also deacetylate non-histone proteins involved in cancer progression and development, in addition to their ability to eliminate the histone acetyl groups. Intriguingly, the primary biological roles of HDACs include encouraging tumor cell angiogenesis, migration, proliferation, and invasion [8]. Consequently, it is hypothesized that HDACis offers significant therapeutic promise for human malignancies [9, 10].

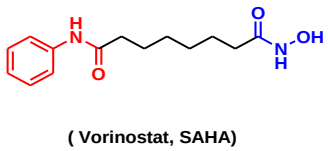
Most HDACis have the common pharmacophore models consisting of 3 moieties: a capping moiety, a zinc-binding group (ZBG), and a linker moiety connecting the two portions [11]. The cap group typically includes a heteroaromatic hydrophobic moiety or aromatic character, which promotes the interaction of amino acids at the enzyme rim and is principally responsible for the selectivity of HDAC isoforms [12]. As ZBG works as a chelating agent for Zn^{2+} at the HDAC active site, its modification can impact the inhibitors' efficiency [13].

1. Pan HDACIs

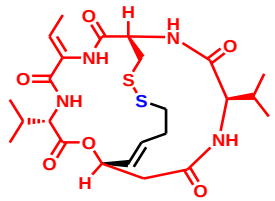
HDACis can be grouped into four major classes based on the ZBG chemical structures: aliphatic acid, benzamides, cyclic peptides & hydroxamates [12, 14]. Hydroxamate-based HDACs are the most studied and potent ones [15]. However, most hydroxamates are pan HDACis utilized for peripheral T-cell lymphoma (PTCL) in individuals with chronic, progressive, or recurrent disease during or after systemic treatments [16].

The FDA had approved six HDACis medications after research efforts in recent years, involving vorinostat (SAHA), romidepsin, belinostat, panobinostat, chidamide and pracrinostat [10, 17]. Monotherapy for solid malignancies is still subjected to certain constraints despite its efficacy against cutaneous and PTCLs and recurrent multiple myeloma. On the other hand, significant adverse effects, such as deep vein thrombosis, leukopenia, pulmonary embolism, anemia, and thrombocytopenia, have been recorded for these medications, which increases concerns about their therapeutic utilization [18].

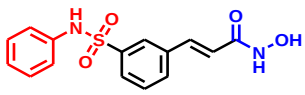
Due to the association between specific HDAC isoforms and various cancer types, cellular localization of particular HDACs & diverse tissue distribution and researchers postulated that isoform-selective HDACis could have a greater therapeutic index & fewer side effects [19].



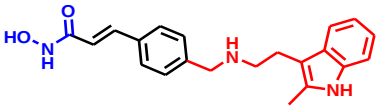
(Vorinostat, SAHA)



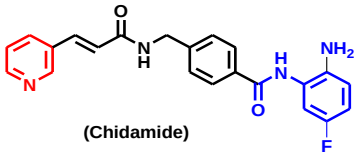
(Romidepsin)



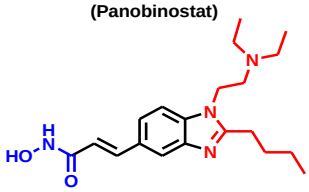
(Belinostat)



(Panobinostat)



(Chidamide)



(Pracinostat)

2. Selective HDACIs

Specific HDAC isoforms were discovered to be related to definite diseases, such as neurodegenerative disorders and malignancies. Selective HDACis are highly required to understand various HDAC isoforms' biological functions better and, more crucially, for developing medicines with more valuable therapeutic index and fewer adverse effects than pan-inhibitors [20, 21].

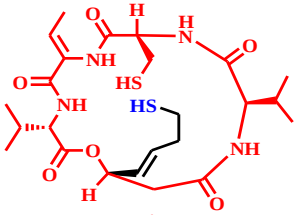
2.1 Class I Selective HDACIs

Class I HDACs' overexpression has been seen in a variety of cancer tissues, including lung, prostate, breast,

stomach, esophagus, and colon. They are essential for managing the cell proliferation & regulation [22].

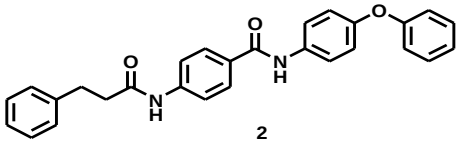
2.1.1 HDAC (1-3)

Elevated HDACs 1-3 expression is associated with reduced patient survival in gastric cancer and nodal tumor spread [6, 23]. On the other hand, HDACs 1-3 are upregulated in human hepatocellular carcinoma (HCCs) [24]. In addition, some colorectal malignancies exhibited high expression of these isozymes [25]. In hormone receptor-negative & poorly differentiated breast cancer, HDAC 2 and 3 are highly expressed, and in hormone receptor-positive breast cancer, HDAC1 is strongly expressed [26, 27]. Moreover, HDAC2 is an independent prognostic factor for prostate cancer, while HDACs 1-3 are highly expressed in prostate carcinomas [28]. Furumai *et al*. reported that Romidipsin potently inhibits HDAC1 and HDAC2 in contrast to HDAC4 and HDAC6 (HDAC1 IC_{50} = 0.036 μM, HDAC2 IC_{50} = 0.074 μM, HDAC4 IC_{50} = 0.51 μM, HDAC6 IC_{50} = 14 μM) [29]. Additionally, it suppresses HDAC1 more effectively under reducing conditions (HDAC1 IC_{50} = 1 nM), indicating that the free thiol analog (compound **1**) liberation as the active species within the cellular environment is a result of the molecule's disulfide bond reduction [30, 31]. Compound 2 is categorized under miscellaneous compounds, which do not fit the standard modular structural mode; compound **2** suppresses HDAC1 preferentially over HDAC3 and HDAC8 (HDAC1 IC_{50} = 1.5 μM; HDAC3 IC_{50} > 100 μM; HDAC8 IC_{50} > 100 μM).



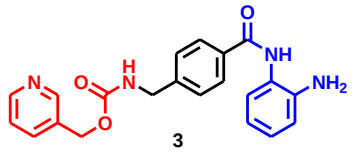
1

It stimulates the dose-dependent elevations in histone H4 acetylation in human colon carcinoma cell line SW620, and the zinc-binding group's absence makes this compound's chemical structure unique. Additionally, it selectively inhibits HDAC1 as it may bind to the HDAC1 allosteric site [32].



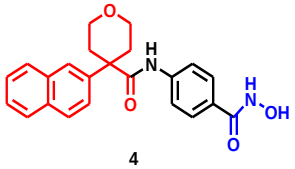
2

Regarding compound **3**, Suzuki and co-workers identified it as an HDAC inhibitor amongst benzamide-based synthetic compounds [33]. It can selectively inhibit HDAC1 (IC_{50} = 181 nM) (102), whereas another group reported that it can inhibit HDAC1 and HDAC3 with identical potency [34]. It can bind to the active sites of HDAC1 & 3 more strongly than that of HDAC8 [34]. Moreover, it does not affect HDAC6 in cells, as it increases the histone acetylation but not tubulin acetylation [35].



3

Compound **4** exhibited significant activity against human class I HDACs (HDAC1 IC_{50} = 0.7 nM), compound **4** (IC_{50} = 0.02-0.1 uM) has less toxicity against normal cells and was 25 times more effective in cytotoxicity against five human cancer cell lines than compound **5** (IC_{50} = 0.3-1.5 uM), the IC_{50} of compound **5** against HDAC1 is reported as 25 nM [36].



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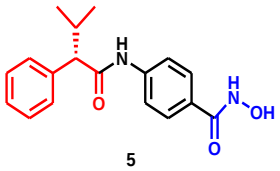
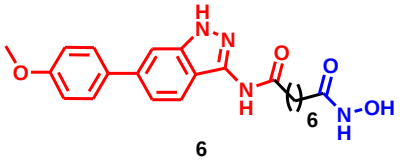


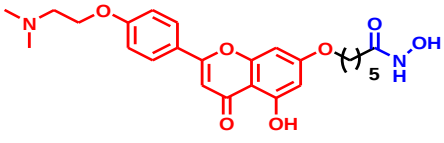
5

Reported HDACi derivatives were developed and exhibited good to excellent HDAC inhibitory activity. HDAC1, HDAC2, and HDAC8 are suppressed by compound **6** with its indazole ring and a six-carbon aliphatic linker (IC_{50} = 2.7, 4.2, and 3.6 nM). It exhibits a more effective antiproliferative effect against HeLa cells & HCT-116 (IC_{50} = 2.1 and 4.4 μM) than the positive control SAHA (IC_{50} =4.9 and 5.0 μM). Western blot examination indicated compound **6** dramatically upregulated histone H3 and acetylated α-tubulin levels [37].



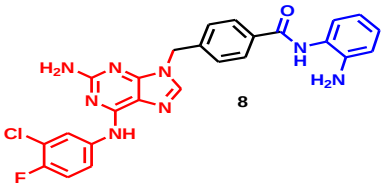
6

Compound **7** with a five-carbon aliphatic linker suppresses HDAC1-3 (IC_{50} = 35 nM) and HDAC6 (IC_{50} = 25 nM), leading to a dose-dependent upregulation of acetylated histone & α-tubulin. Compound **7** displayed significant antiproliferative effects against numerous solid tumor cells, as breast cancer cells resistant to SAHA. It may also reduce the STAT3 activation by HDAC inhibition in some breast cancer cells, limiting the pro-survival protein quantities in tumor cells and improving the antitumor activity mediated by STAT3 signaling *in vivo* [38].



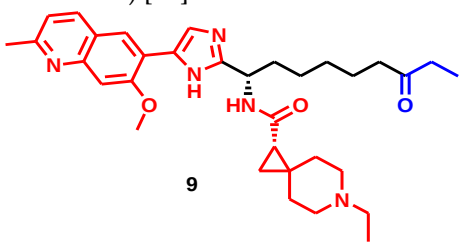
7

Compound **8** is one of a variety of HDAC inhibitors that exhibited potent inhibitory effects on HDAC1, 2, & 3 (IC_{50} = 108, 585, and 563 nM), which may be translated into higher anticancer impacts in breast cancer mouse models of human MDA-MB-231. It had shown potent antiproliferative activity against negative liver cancer cells HepG2 and triple-breast cancer cells MDA-MB-468, MDA-MB-23139.



8

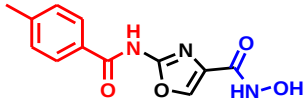
Yu and co-workers developed HDAC inhibitors that target HDAC1-3 (IC_{50} = 0.3-0.4 nM) in particular. Compound **9**, with an imidazole scaffold and an ethyl ketone ZBG, indicates a highly effective HDAC1-3 inhibitor with superior selectivity over HDAC6 & 8. Additionally, It demonstrates an increased serum shift in cellular potency and a reduction in hERG activity (cardiovascular risks) [40].



9

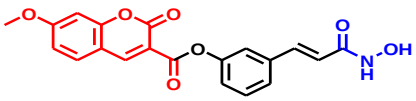
2.1.1.1 HDAC1 selective inhibitors

Human liver cancer cell lines & HCCs show high HDAC1 expression [41]; HDAC1 is also overexpressed in diffuse large B cell lymphoma (DLBCL), which is accompanied by poor survival [42]. Also, in myeloma, HDAC1 overexpression is associated with poor outcome [43]. Anh et al. developed a set of hydroxamic acids in the sub-micromolar IC_{50} range (0.010-0.131 uM) with HDACs inhibitory properties. The exemplary compound **10** inhibits HDAC1 with greater potency (IC_{50} = 0.01μM) than SAHA (IC_{50} = 0.025μM); biological evaluation showed that this hydroxamic acid compound generally exhibited good cytotoxicity against three human cancer cell lines (SW620, colon; PC-3, prostate; NCI-H23, lung cancer), with IC_{50} values in the low micromolar range and comparable to that of SAHA [44].



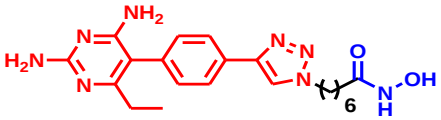
10

Among a variety of developed HDACis, compound **11** with hydroxamic acid as ZBG demonstrated potent antiproliferative activity against HeLa cells (IC_{50} = 0.23 μM) and full inhibitory activity against HDAC1 (IC_{50} = 0.19 μM) [45].



11

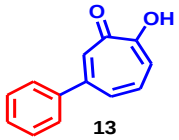
Wu *et al*. developed several HDACis. Compound **12** with a six-carbon aliphatic linker exhibited significant inhibitory effects against HDAC1 (IC_{50} = 45 nM) & HDAC6 (IC_{50} = 17 nM) in cell-free assays and induced intracellular inhibition of STAT3 pathway & HDACs; this compound is cytotoxic to MDA-MB-231, a TNBC cell line that is highly STAT3-dependent [46].



12

2.1.1.2 HDAC2-selective Inhibitors

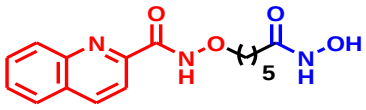
Medulloblastoma with a poor prognosis is characterized by HDAC2 overexpression [47]. In addition, HDAC2 inactivation inhibits tumor cell proliferation *in vitro* and *in vivo.* Abundant HDAC2 expression is reported in lung cancer tissues [48]. Additionally, pancreatic ductal adenocarcinoma (PDAC) had a significant HDAC2 expression [49]. In sporadic colorectal malignancies, mutations in HDAC2 result in the decrease of protein expression [50]. In addition, HDAC2 is strongly expressed in nodal lymphomas, which have a poorer survival rate [51]. Compound **13** is among a published series of HDAC2-selective inhibitors with a tropolone scaffold that exhibited significant HDAC2 selectivity (0.06 nM). The antiproliferation assay can also potently suppress the growth of several tumor cell lines; it inhibits the growth of T-cell lymphocyte cell lines [52].



13

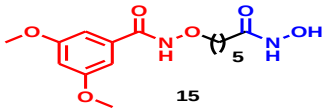
Avelar *et al.* revealed enhanced inhibitors with solid activity against bortezomib-resistant leukemia cells and cisplatin-resistant head-and-neck malignant cells. A substantial inhibitory effect on HDAC2 (IC_{50} = 92 nM) and HDAC6 (IC_{50} = 25 nM), but only moderate impacts on HDAC8 (IC_{50} = 9.7 μM) and negligible effects on HDAC4 (IC_{50} = 100 μM) is attained by compound **14,** which was found to be a potent inhibitor of HDACs whole cell assays

(IC_{50} = 0.25 μM) and Cal27 cells in the MTT assay (IC_{50} = 0.25 μM) [53].



14

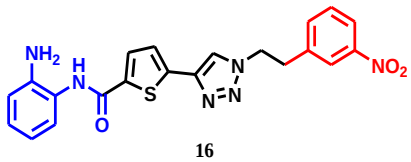
Asfaha *et al*. synthesized compound **15**, which was the most effective among the synthesized compounds. The histone H3 and α-tubulin acetylation in Cal27CisR & Cal27 verified its dual inhibitory impact on HDAC2 (IC_{50} = 60 nM) and HDAC6 (IC_{50} = 30 nM) [54].



15

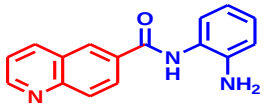
2.1.1.3 HDAC3-selective Inhibitors

DLBCL exhibited HDAC3 overexpression [55]. High HDAC3 expression is also associated with enhanced stage IV metastatic melanoma survival [56]. A series of HDAC3 selective inhibitors was designed by Suzuki *et al*., who revealed that compound **16** with submicromolar IC_{50} (260 nM) is an effective HDAC3 inhibitor. However, even at 100 μM, it did not inhibit other HDAC isozymes; it induced a dose-dependent selective increase of NF-κB acetylation in human colon cancer HCT116 cells, indicating selective inhibition of HDAC3 in the cells [57].



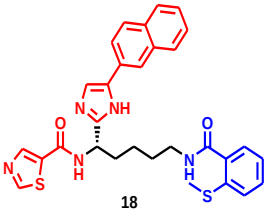
16

The linker-less benzamide-based lead compound **17** demonstrated modest selective HDAC3 inhibition (IC_{50} = 0.56 μM) over class I HDACs, compound **17** induced apoptotic cell death in Annexin-V/FITC-PI assay and caused cell cycle arrest at G2/M phase of the cell cycle in B16F10 cells [58].



17

A set of compounds with a 2-substituted benzamide ZBG that appeared to target HDAC3 selectively was designed. Compound **18** is a selective and potent HDAC3 inhibitor (IC_{50} = 30 nM and more than 300-fold selectivity over other HDAC). Notably, its analog, compound **19,** was revealed to maintain HDAC's efficacy (HDAC3 IC_{50} = 7.6 nM).



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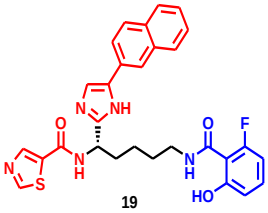


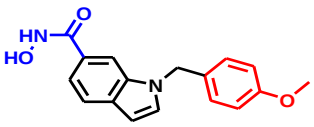
19

This series of HDAC3 selective inhibitors served as tool compounds for investigating the minimal set of HDAC isoforms that must be inhibited for the HIV latency activation in a Jurkat 2C4 cell model [59].

2.1.2 HDAC8 Selective Inhibitors

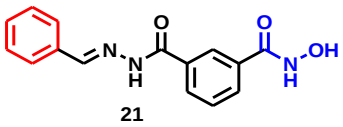
In several malignancies such as breast, lung, colon, pancreatic, neuroblastoma, and myeloid leukemia, HDAC8 overexpression is observed [60]. In addition, hepatocellular carcinoma and breast cancer exhibit a pronounced upregulation of HDAC8 [61]. In neuroblastoma, high levels of this isozyme correspond with advanced disease stage and poor prognosis [62, 63].

Compound **20** was reported as a potent HDAC8-specific inhibitor (IC_{50} = 0.01 μM) with > 200-fold selectivity over other HDAC isoforms. It contains an indole moiety that triggers apoptosis in tumor cells generated from T cells and does not increase histone or tubulin acetylation. Its selectivity for the HDAC8 enzyme may be explained by the conjugation of 4-methoxybenzyl to the enzyme sub-pocket of the HDAC8; it also induced caspase-dependent apoptosis in cell lines derived from T-cell lymphomas or leukemias, but not in other hematopoietic or solid tumor lines [64].



20

In enzymatic studies against HDAC2, HDAC3 & HDAC8, the synthesized compounds **21, 22** & **23** demonstrated considerable selectivity towards isoform 8 (IC_{50} = 0.052, 0.029 and 0.023 μM, respectively). The compounds' activity/selectivity profiles were identical despite their cap groups exhibiting distinct stiffness and bulkiness.



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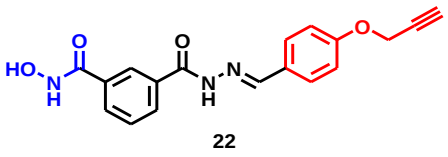

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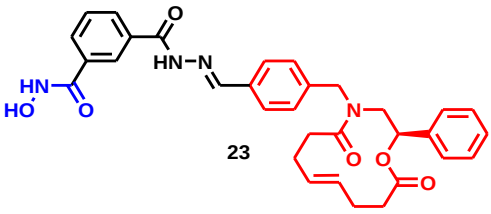
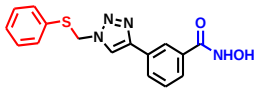


23

Compounds **24** and **25** were reported as effective HDAC8 inhibitors (IC_{50} = 0.070 and 0.10 uM, respectively). The phenyl dimethyl group of compounds **24** conjugates to a distinct HDAC8 hydrophobic pocket, and for its potency and selectivity,



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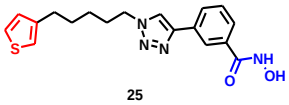

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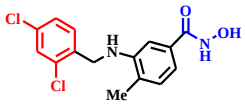

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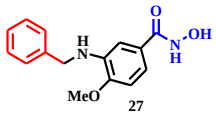

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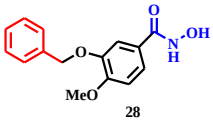
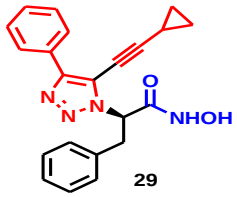


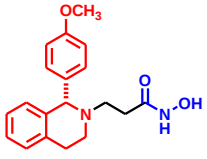
28

the orientation of the phenyl dimethyl and hydroxamate moieties (fixed by the triazole moiety) is crucial; the inhibitors caused selective acetylation of cohesin in cells and exerted growth-inhibitory effects on T-cell lymphoma and neuroblastoma cells (GI50 = 3–80 μM) [65]. Heimburg and co-workers developed compounds **26**, **27**, and **28** with enhanced inhibitory potency against HDAC8 with (IC_{50} = 0.04, 0.017 and 0.03 μM, respectively). They inhibit tumorigenesis as they were shown to be efficient in the up-regulation of the neurofilament-positive neurite-like structures & differentiation marker genes outgrowth; the cytotoxicity of the compounds was tested against a human embryonic kidney cell line (HEK293) at a concentration of 50 μM, it showed only relatively weak cytotoxicity at the used concentration [66]. Compound **29** is among the most potent and selective HDAC8 inhibitors (IC_{50} = 0.0008 μM). SAR of designated compounds illustrated that small hydrophobic groups, such as cyclopropane, were beneficial and afforded more significant inhibition [67].



29

Compounds **30** and **31** are among a unique family of HDAC8 inhibitors; they displayed the highest HDAC8 efficacy and selectivity over HDAC1 at 82 and 55 nM, 330 and 135-fold selectivity over other class I isoforms. Their cytotoxicity was assessed in neuroblastoma cell lines, and their selectivity was validated in SH-SY5Y cells, where neither compound increased α-tubulin & histone H3 acetylation [68].



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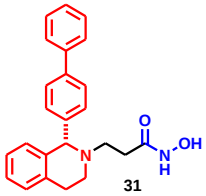
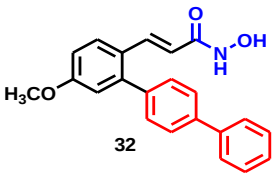


31

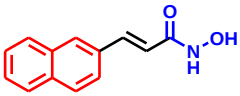
Compound **32** (HDAC8 IC_{50} = 27.2 nM) was designed with antiproliferative activities against multiple human lung cancer cell lines (CL1-5, H1299 & A549); it demonstrated comparable cytotoxicity against human lung CL1-5 cells to that of SAHA, but no significant cytotoxicity against normal IMR-90 cells [69].



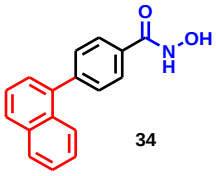
32

Hrubec and co-workers designed a six-membered class of compounds. Enzymatic assay screening discovered powerful HDAC8is, compounds **33** (IC_{50} =

0.7 μM) and **34** (IC_{50} = 0.3 μM) are > 100-fold selective for HDAC8 compared to their isoforms [70].

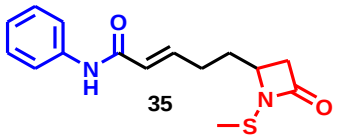


33



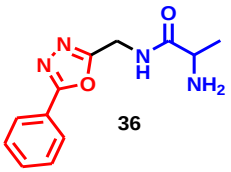
34

A set of N-thiomethyl-azetidinones containing compounds that are HDAC8 selective inhibitors in the micromolar range were developed. Compound **35** had moderate inhibitory activity (IC_{50} = 4.53 μM) in comparison to other HDACs (IC_{50} > 1000 μM). As revealed by computational analysis, this compound has a low inhibitory effect because the carbonyl of azetidine-2-one can chelate zinc in a monodentate manner, while the Sulphur atom is included in the interaction with HDAC8 Trp141 [71]



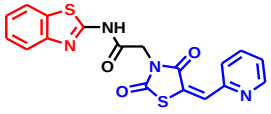
35

Compound **36** with an oxadiazole moiety inhibited the HDAC8 expression but no other class I HDACs; it inhibited the growth of MDA-MB-231 and MCF7 breast cancer cells through p21 induction and CDK1 proteins inhibition, with a lower IC_{50} of 230 and 1000 nM, respectively [72, 73]. Structurally selective HDAC8 compounds containing *N*-substituted thiazolidinediones moiety were synthesized.



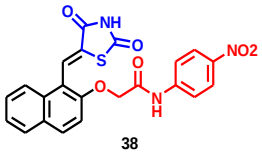
36

The non-hydroxamate compound **37** was the most potent HDAC8 inhibitor (IC_{50} = 9.3 μM). Moreover, it was much less cytotoxic to human fibroblasts (HS27) (CC50 = 105.0 μM) and normal WBCs (CC50 = 104.2 μM) [74].



37

A unique family of non-hydroxamate derivatives of 5-naphthylidene-2,4-thiazolidinedione was designed. Compounds **38** and **39** were identified as the most effective and selective HDAC8 inhibitors, with IC_{50} values of 2.7 and 6.3 μM, respectively [75].



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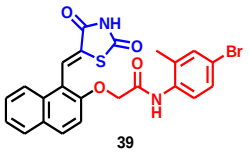
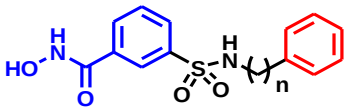


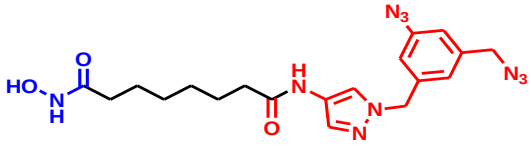
39

A novel series of N-hydroxy-3-sulfamoylbenzamide-based HDAC8 selective inhibitors were synthesized. Compounds **40, 41** & **42** with nanomolar IC_{50} values of 50, 80, and 60 nM demonstrated efficient HDAC8 inhibition. They additionally exhibited specific antiproliferative effects on two T-cell leukemia cell lines [76].



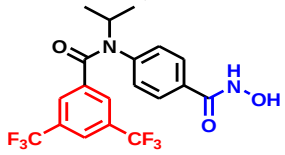
40: n = 0
41: n = 1
42: n = 2

Neelarapu *et al*. developed efficient pyrazole-based HDAC8 inhibitors; compound **43** was the most effective amongst these agents and displayed neuroprotective and antiproliferative effects at micromolar levels *via* nuclear HDAC8 inhibition and was eight-fold more active towards HDAC8 than HDAC3 (IC_{50} = 17 nM) [77].



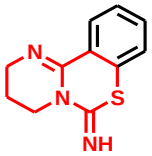
43

A variety of compounds that bind specifically to HDAC8 catalytic channels were developed. Compound **44** with a benzanilide scaffold demonstrated up to 410-fold HDAC8 selectivity over other HDACs and high *in vitro* HDAC8 activity (IC_{50} = 23 nM) [78].

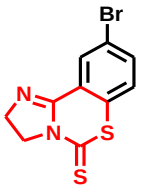


44

Compound **45** was identified as a highly selective HDAC8 non-hydroxamate inhibitor that lacks classic zinc binding groups but binds to the enzyme's active site (IC_{50} = 0.011 μM). Although, it degrades rapidly in the presence of glutathione (GSH) [79]. The modified compound **46** exhibited significant selectivity for HDAC8 (IC_{50} = 0.26 μM) compared to HDACs and double-digit nanomolar potency, colony assay using SK-N-BE(2)-C neuroblastoma tumor cells and treating them with different concentrations of indicated compounds showed great antiproliferative activity [80].



45



46

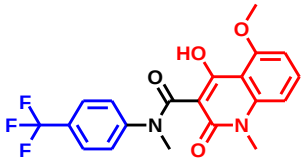
2.2 Class II selective HDACIs

2.2.1 Class IIa selective HDACIs

2.2.1.1 HDAC4 Selective Inhibitors

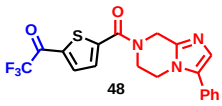
HDAC4 is overexpressed in gastric carcinoma cells relative to surrounding normal tissues [81]. Its high expression is related to T-cell adult acute lymphoblastic leukemia (ALL) and elevated initial leukocyte count [82].

Compound **47**, an orally active antiangiogenic medication in phase III clinical trials for castration-resistant prostate cancer treatment, was identified as a negative allosteric HDAC4 modulator (IC_{50} = 30 nM) that interacts with the carboxamide moiety at the HDAC4' ZBG [83].



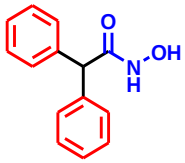
47

Compound **48** is amongst a set of 5-(trifluoroacetyl) thiophene-2-carboxamides which was ten times more selective for HDAC4 & 6 than class I HDACs and was identified as a moderate HDAC4 inhibitor (IC_{50} = 320 nM) [84].



48

Tessier *et al*. identified a diphenylmethylene hydroxamic acids group in the sub-micromolar range on HDAC4 (IC_{50} = 0.75 μM), HDAC5 (IC_{50} = 0.14 μM) & HDAC7 (IC_{50} = 0.39 μM), compound **49** showed potent inhibitory activities. Compound **50**, an analog of rigidified oxygen, exhibited comparable inhibitory effects on HDAC4 (IC_{50} = 0.25 μM), HDAC5 (IC_{50} = 0.11 μM), & notably higher selectivity for HDAC7 (IC_{50} = 0.05 μM) [85].



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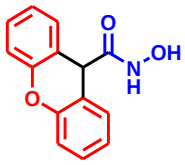
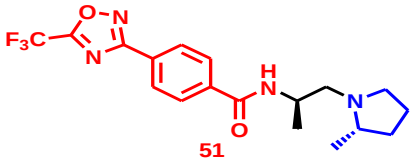


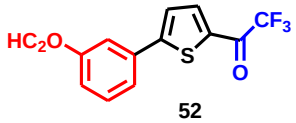
50

Compound **51** was identified as a potent 1,2,4-oxadiazole-based HDAC4 inhibitor with IC_{50} = 0.04 μM; it is used in preclinical models of Huntington's disease [86].



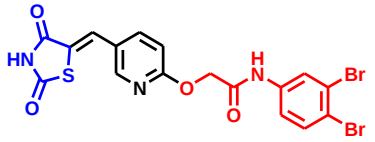
51

Ontoria and co-workers designed a thiophene-based HDAC4 inhibitor, compound **52** showed potent HDAC4 inhibitory activity (IC_{50} = 310 nM) with enhanced stability in HCT116 cancer cells and 40-fold selectivity over HDAC1 [87].



52

Potent non-hydroxamate compounds exhibiting HDAC4 inhibitory activities were designed. Compound **53** (IC_{50}=4.2±1 μM), **54** (IC_{50} = 0.75±0.03 μM), **55** (IC_{50} = 4.9±0.5 μM) and **56** (IC_{50} = 2.3±0.5 μM). In addition, compounds **54** & **55** were demonstrated to be the most potent antiproliferative agents in breast cancer MDA-MB-231 cells and lymphoblastic leukemia (CCRF-CEM) [88].



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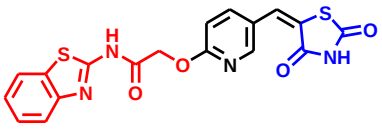

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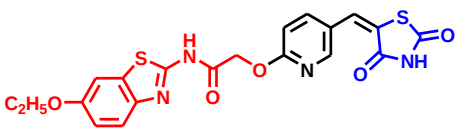

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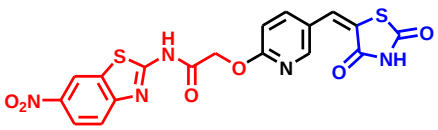


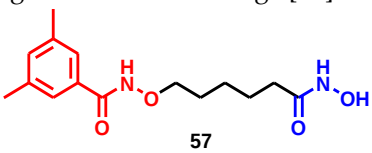
56

2.2.1.2. HDAC5 selective inhibitors

HDAC5 expression is accompanied by a poor outcome in lung cancer and frequently diminished in tumors such as acute myeloid leukemia (AML) and colon cancer [89].

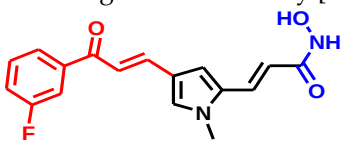
It is upregulated in medulloblastomas with a high risk of mortality, and its expression is associated with a poor outcome 90. *In vitro* & *in vivo*, HDAC5 knockdown decreases tumor cell proliferation and promotes apoptosis; HDAC5 is upregulated in HCC tissues [91].

Compound **57** was reported, which exhibited comparable effects to vorinostat on suppression of cellular HDACs in a pan-HDAC assay but exhibited more excellent cytotoxic effects against the human cancer cell lines MDA-MB231, Kyse510, Cal27 & A2780. In the nanomolar range, it inhibits HDAC4 (IC_{50} = 11.9 nM) & HDAC5 (IC_{50} = 4.22 nM), whereas TSA & vorinostat suppress HDAC4 & HDAC5 in a higher micromolar range [92].



57

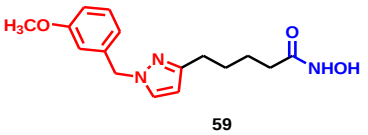
Nebbioso and co-workers synthesized compound **58**, which impairs myogenesis. *In vivo*, it appears to suppress HDAC in a tissue-selective manner. In contrast, it reduces HDAC4 and HDAC5 activities in the heart and skeletal muscle without affecting HDAC3 activity [93].



58

2.2.1.3. HDAC7 selective inhibitors

HDAC7 overexpression is related to a bad prognosis in pancreatic cancer, whereas HDAC7 knockdown suppresses the development of tumor cells [94]. Additionally, human colorectal cancer exhibited HDAC7 upregulation [95]. Compounds **59**, **60**, and **61** were investigated using pharmacophoric modeling tools. Four unique chemical properties may be responsible for HDAC7's inhibitory effect (IC_{50} = 0.311, 0.355, and 0.360 µM, respectively), according to a docking analysis of the active site of the HDAC7 enzyme. These are hydrophobic ligands, hydrogen bond donors, hydrogen bond acceptors & aromatic ring [96].Wang and co-workers reported some HDAC7 inhibitors. Among these, compound **62** (IC_{50} = 12 nM) and compound **63** (IC_{50} = 20 nM) in a sub-nanomolar range displayed the most potent inhibitory activities on HDAC7 in neuroblastoma cell lines [97].



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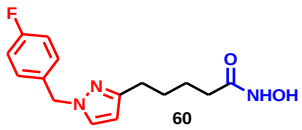

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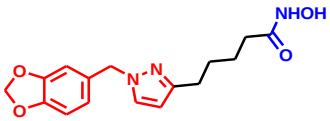

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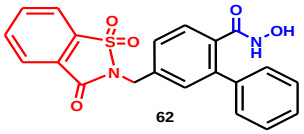
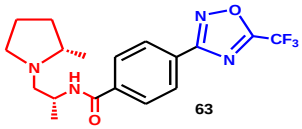
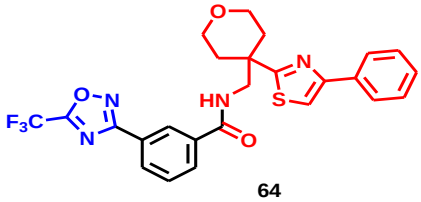


62



63

A unique compound with a non-classical chelating zinc binding group, trifluoro-methyloxadiazole (TFMO), was reported, and compound **64** exhibited good selectivity towards HDAC7 (IC_{50} = 0.036 µM) [98].



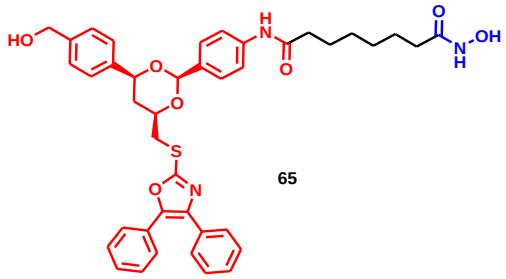
64

2.2.2 Class IIb Selective Inhibitors

2.2.2.1 HDAC6 Selective Inhibitors

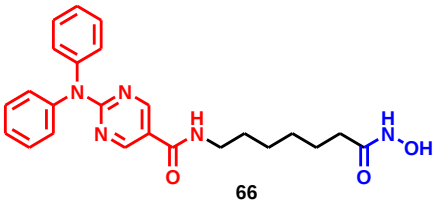
HDAC6 knockdown enhances HCC angiogenesis [99], and its high expression is reported in pancreatic cancer tissues, DLBCL, and PTCL [100]. Also, its overexpression is found in AML [101]. A high HDAC6 level is associated with a favorable prognosis in DLBCL but a poor prognosis in PTCL [102].

Compound **65** was the first reported HDAC6 inhibitor (IC_{50} = 4 nM). It had distinct effects on HDAC1, 6, & 8, primarily derivatives of the surface variation between class I and II HDACs. However, its increased lipophilicity rendered it more valuable as a chemical agent than a potential medication [103].



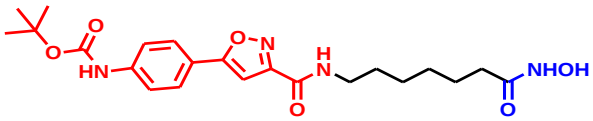
65

Compound **66** is the first selective HDAC6 inhibitor to enter clinical trials (IC_{50} = 5 nM). Its low doses in combination with lenalidomide or bortezomib can elicit synergistic therapeutic results in multiple myeloma treatment [104].



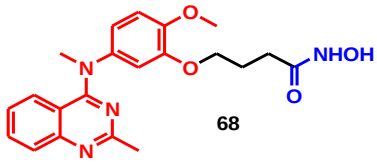
66

An aryl-substituted isoxazole-containing powerful HDACi was reported. Compound **67** exhibited an excellent 2 μM potency against HDAC6. The carbonyl group of the Boc group may interact with His499, which may be essential for placing the cap residue on the protein surface [105].



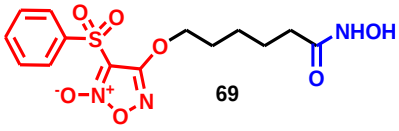
67

Using quinazoline as the cap area, selective HDAC6 inhibitors were reported. Keeping the HDAC6 selectivity and activity requires a hydroxamic acid on C-3 and a methoxy group addition on C-4, as revealed by the SAR analysis. In this set, compound **68** was the most potent selective inhibitor (IC_{50} = 17 nM). This compound also showed outstanding low nanomolar antiproliferative activity against solid and hematological malignancies [106].



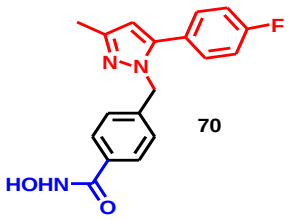
68

A series of phenylsulfofuroxan-based hydroxamates that inhibit HDAC and donate NO was designed. Compound **69**, the most effective hybrid, exhibited potent HDAC6 activity (IC_{50} = 7.4 nM); additional research revealed that this compound showed more oral anticancer effectiveness than SAHA *in vivo* and generated a considerably more significant apoptotic effect and G1 phase arrest in HeLa cells [107].



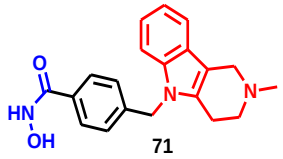
69

Compound **70** was the most selective HDAC6 inhibitor (IC_{50} = 20 nM) among a series of phenyl-pyrazole-containing HDACis developed and synthesized. Analysis of the SAR revealed that placing the linker group at the 1′ position of pyrazol provided the most outstanding selectivity. Furthermore, it was six times more effective than vorinostat in HepG2 cells [108].



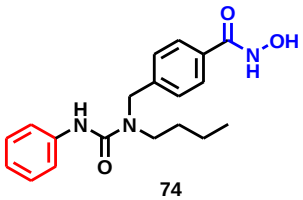
70

Carbazole-based hydroxamic acid derivatives with an aralkyl linker were developed. Compound **71** had the most effective HDAC6 inhibitory action (IC_{50} = 15 nM). According to the subsequent SAR, substitutions at the 6-, 7-, 8-, and 9-positions of the cap group did not improve their selectivity despite the advantages of the presence of aromatic functionalities introduced at the 2-position [109].



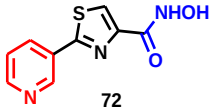
71

Compound **72**, with an IC_{50} of 300 nM, is a reported HDAC6 inhibitor. According to SAR studies, thiazole derivatives were considerably less potent and selective than oxazole-containing structures, although para-position substitutions were more selective. Furthermore, compound **73** (4-bromophenyl substituted oxazole hydroxamate) was the series' most potent analog (IC_{50} = 59 nM) [110]. The first HDAC6-selective inhibitors that reduce melanoma cell proliferation were prepared by Bergman *et al*. According to SAR analysis, compounds with a branched linker group displayed improved HDAC6 selectivity and potency. Compound **74** has low nanomolar inhibitory efficacy against HDAC6 (IC_{50} = 5.02 nM) and 600-fold selectivity relative to HDAC1 inhibition (IC_{50} = 3.02 μM) [111].

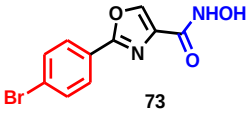


74

Compound **75** was the most effective HDAC6 inhibitor amongst a set of selective HDAC6 inhibitors utilizing peptide-based branched cap groups, which exhibited a nanomolar inhibitory activity (IC_{50} = 1.59 nM) [112].



72



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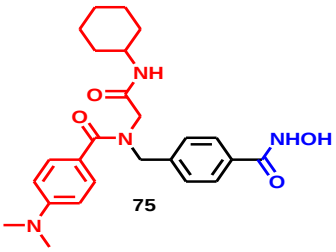
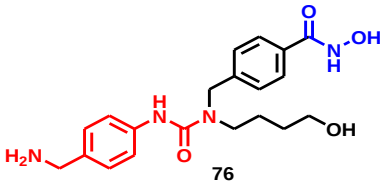


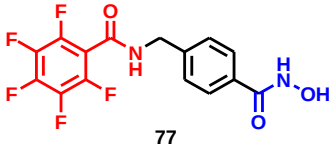
75

A series of HDAC6 selective inhibitors utilizing *in silico* simulations was developed. The most potent compound **76** represents a new class of selective HDAC6 inhibitors (IC_{50} = 0.4 nM) with 100-1000-fold selectivity over other HDACs isozymes and sub-nanomolar HDAC6 inhibitory activity [113].



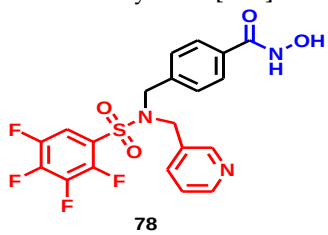
76

Compound **77** was discovered to be a selective HDAC6 inhibitor with low nanomolar efficacy (IC_{50} = 5.92 nM). It exhibits little cytotoxicity against non-cancerous cells and an excellent safety profile. It is very effective against several blood cancer cell lines [114].



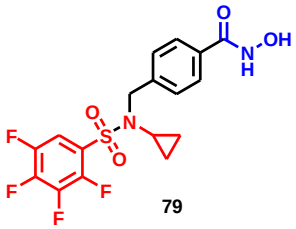
77

A 158-fold HDAC6 selectivity over other HDACs was exhibited by compound **78**. The addition of a 3-pyridylmethyl group to the cap results in attaining new selectivity & affinity interactions in the active site of HDAC6 (IC_{50} = 2 nM), leading to a considerable increase in activity, as determined by SAR [115].



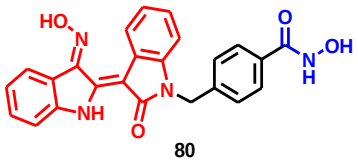
78

Compound **79** (HDAC6 inhibitor, IC_{50} = 8.5 nM) was more effective in treating T-cell prolymphocytic leukemia than other hematological malignancies. It exhibits a favorable therapeutic efficacy in non-transformed cell lines [116].



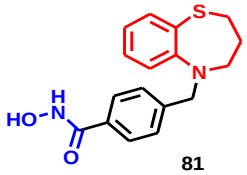
79

Many HDAC6 inhibitors based on indirubin moiety were introduced. Compound **80** is an effective, selective HDAC6 inhibitor (IC_{50} = 7 nM) with 29-fold for HDAC6 isoform selectivity over the HDAC2 isoform (IC_{50} = 205 nM) [117].



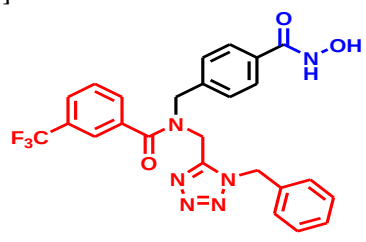
80

Compound **81** was amongst a group of selective HDAC6 inhibitors developed by Guo *et al*. It exhibits 141-fold selectivity over HDAC1, excellent HDAC6 selectivity (IC_{50} = 1.8 nM) & low nanomolar potency [118].



81

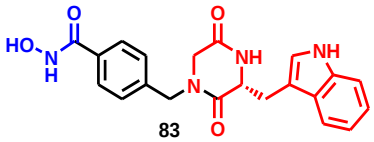
Rebing and colleagues designed compound **82** (IC_{50} =30 nM). The tetrazole ring strengthens the compound's stiffness, as revealed by SAR research. In addition, it could considerably boost the apoptosis-inducing actions of the proteasome inhibitor bortezomib. Its combination with epirubicin and daunorubicin significantly increased cytotoxicity, as demonstrated by high-throughput drug screening [119].



82

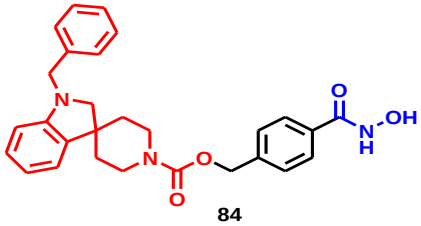
Chen *et al*. produced a variety of new 2,5-diketopiperazine (DKP) compounds as particular HDAC6 inhibitors. Most of them exhibited low nanomolar activity

against HDAC6. Compound **83** (IC_{50} = 0.73 nM) is the most potent analog with superior HDAC6 selectivity relative to other derivatives [120].



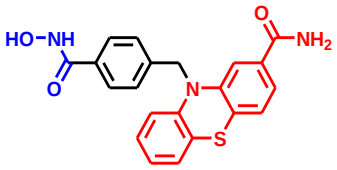
83

The most efficient and selective HDAC6 inhibitor is compound **84** (IC_{50} = 48.5 nM), which is one of a group of HDAC6 selective inhibitors found by Saraswati *et al*. This compound could increase tubulin acetylation without significantly affecting the histone acetylation status, according to studies utilizing Western blotting [121].



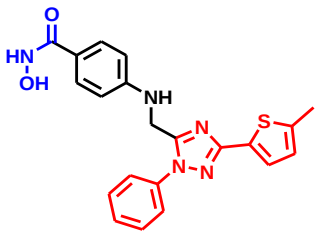
84

Compound **85**, a selective HDAC6 inhibitor (IC_{50} = 4.6 nM) with a phenothiazine scaffold and hydroxamic acid as ZBG, was reported as it can stimulate neurite development without damage to nerve cells [122].



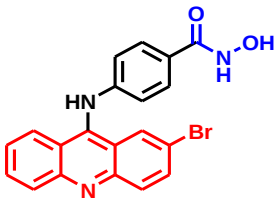
85

Among various triazole-based HDAC6 inhibitors, compound **86** had 128-fold selectivity over HDAC1 and the highest inhibitory activity against HDAC6 (IC_{50} = 30.6 nM). It might dose-dependently enhance the amount of acetylated α-tubulin but did not affect the acetylated histone H3 in MGC803 cells [123].



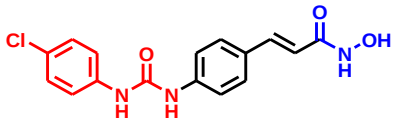
86

Compound **87**, with aryl-hydroxamate pharmacophore designed by Tseng and colleagues, it exhibited excellent HDAC6 selectivity in the nanomolar range (IC_{50} = 26 nM) [124]. A set of urea-based cinnamyl hydroxamate



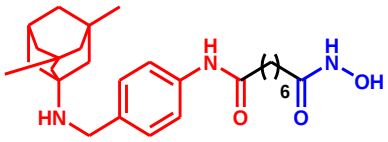
87

compounds as potential anticancer HDAC6 inhibitors was developed. Compound **88** exhibited potent, selective HDAC6 inhibition (IC_{50} = 8.1 nM) and potent antiproliferative activity against hematological malignancies [125].



88

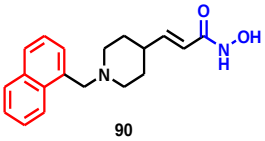
A memantine-based series of compounds as HDAC6 selective inhibitors were reported; the memantine cap group has a brain penetration capability. Compound **89** is this series's most potent selective HDAC6 inhibitor at nanomolar dosage (IC_{50} = 5.42 nM), exhibiting significant cell growth-inhibiting actions against glioma cell lines [126].



89

2.2.2.2. HDAC10 selective inhibitors

In stage 4 neuroblastoma, high HDAC10 expression is associated with poor overall patient survival [127]. Low HDAC10 expression is related to poor outcomes in lung cancer and is also regarded as a sign of poor prognosis in gastric cancer [128]. Patrik *et al*. developed the hydroxamate-based compounds **90** & **91**, which were evaluated for their selectivity in AML cells harboring the FLT3-ITD oncogene. They were demonstrated to be nanomolar HDAC10 inhibitors with good selectivity over HDAC6 (IC_{50} = 20, 58 nM, respectively) and negligible effect on class I HDACs. Nonetheless, they benefit from not harming normal human kidney cells [129].



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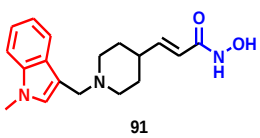
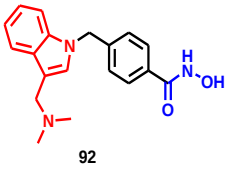


91

High-potent selective HDAC10 inhibitors were synthesized. Compounds **92** & **93** have high selectivity against class I HDACs, good selectivity against HDAC6,

and excellent potency against HDAC10 (IC_{50} = 8.3, 8.4 nM, respectively).



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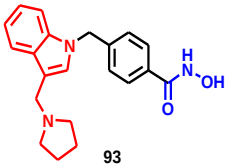
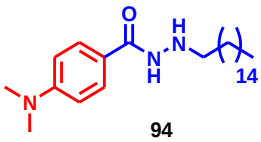
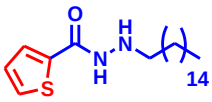


93

These compounds with a strategically positioned amino group displayed enhanced hydrogen bonding with the gatekeeper residue Glu272 and Glu22 of HDAC10 isozyme [130].



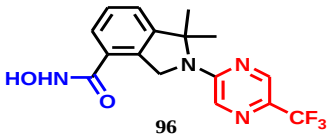
94



95

2.3. Class IV Selective Inhibitors

In malignancies such as renal pelvis urothelial carcinoma, HCC, and breast cancer, HDAC11 is overexpressed [131]. Two potent HDAC11 inhibitors were synthesized, compounds **94** (IC_{50} = 0.91 μM) and **95** (IC_{50} = 0.83 μM), active in cells and inhibited HDAC11 substrate without inhibiting other HDACs. Regarding compound **95**, they investigated the necessity of carbohydrazide, a zinc chelating group, for HDAC11 suppression. Substituting an amide for the carbohydrazide eliminates the compound selectivity toward HDAC11 [132]. Martin *et al*. identified N-hydroxy-2-arylisoindoline-4-carboxamides as practical and specific HDAC11 inhibitors. Compound **96** potently inhibits HDAC11 isozyme (IC_{50} = 3 nM) at nanomolar concentrations [133].



96

Conclusion

HDACs are crucial for controlling chromatin structure and gene expression, making them attractive targets for cancer therapy. While pan HDACis have shown efficacy against certain cancers, their utilization is restricted by adverse effects. Selective HDACis development offers a promising alternative, as specific HDAC isoforms are associated with different types of cancer. By targeting these isoforms, selective HDACis can provide more precise therapeutic effects with reduced side effects. Several selective HDACis have exhibited excellent potency and demonstrated selective cytotoxicity against cancer cells while sparing normal cells. These findings highlight the potential of selective HDACis in improving cancer treatment outcomes. Further research and development of isoform selective HDACis are warranted to enhance their therapeutic index and expand their application in cancer therapies.

Ethical consideration:

All the participants in this study gave their informed permission.

Conflicts of Interest

No conflicts of interest are disclosed.

Abbreviation List

HDACs	Histone deacetylases
HDACis	Histone deacetylase inhibitors
IC_{50}	Half-maximal inhibitory concentration
NAD^+	Nicotinamide adenine dinucleotide
Zn^{2+}	Zinc
SIRT	Sirtuin
ZBG	Zinc binding group
PTCL	Peripheral T-cell lymphoma
SAHA	Suberoylanilide hydroxamic acid

HCCs	Human hepatocellular carcinoma
μM	Micrometer
nM	Nanometer
α	Alpha
STAT3	Signal transducer and activator of transcription 3
hERG	Human ether-a-go-go-related gene
DLBCL	Diffuse large B cell lymphoma
PDAC	Pancreatic ductal adenocarcinoma
MTT assay	3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
NF-κB	Nuclear factor kappa B
HIV	Human immunodeficiency virus
GI_{50}	Growth inhibition of 50% of cells.
HEK293	Human Embryonic Kidney
SAR	Structure-activity relationship
CDK1	Cyclin-dependent kinase 1
HS27	Human skin fibroblast cell line
CC_{50}	Half maximal cytotoxic concentration
WBCs	White blood cells
GSH	Glutathione
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
TSA	Trichostatin A
DKP	Diketopiperazine

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