2. LITERATURE REVIEW

1. Hwan Mook Kim et al (2007); reported Modification of cap group in δ-lactam-based histonedeacetylase inhibitors.\(^71\)

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By substitution on benzoyl and aromatic groups on δ-lactam containing HDAC inhibitors (1) were evaluated for anti proliferative and anti cancer activity. These substituted compounds have very potent HDAC inhibitions and shows the strong development inhibitory activity to human cancer cell lines PC3, ACH N, NUGC-3, HCT-15, and MDA-MB-231. Design and synthesis of (1) HDAC include structural properties of δ -lactam cyclic ring as linker field between outside identification of cap group & Zn\(^{+2}\) adhesive hydroxamate province. The compound with two methylene units between Zn\(^{+2}\) binding hydroxamate & δ lactam moiety has shown strong HDAC inhibitory function. The extent between δ lactam core & hydrophobic cap group is bearable to the inhibitory activity.

2. Steve Price et al (2007); have reported Identification and optimization of a series of substituted 5 (1H-pyrazol-3-yl)-thiophene-2-hydroxamic acids as potent histone deacetylase (HDAC) inhibitors.\(^72\)

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An optimized analogues of phenyl-tethered HDAC inhibitors display important strength in *in vitro* cells and cell abundance assays. Fictionalization of phenyl group of hydroxamic acids from series has lead to increase in the activity, which possessed solitary digit nano molar strength in the HDAC assay, substitutional nano molar activity in MCF-7 cell differentiation assay. The most comprehensively exemplified group of inhibitor is depends upon hydroxamic acid molecule, which is acknowledged Zn$^{2+}$ binding group has observed. A brilliant bioavailability with better plasma coverage was observed for compounds in the mice via an intra muscular route.

3. Lynda Loudni et al (2007); reported 1,4-benzodiazepine-2,5-dione-based HDAC inhibitors.  

With the plan to find out HDAC inhibitors with high power and better protection profile, a small library depends on a N-hydroxy-(4-oxime)-cinnamide (4) gibbet has designed. Synthesis of these new compounds subjected to *in vitro* cytotoxic activity on three cancer cell lines, NB 4, H 460 and HCT 116, and their inhibitory movement against class I, II and IV has also reported. Quite a lot of 4-oxime substitutes established inhibitory function on HDAC 6 and HDAC 8 joined to a better selectivity profile. Histone deacetylase (HDACs) are concerned in the remodeling of chromatinoid and play a vital role in the genetic regulation and expressions have observed. HDACs catalyze deletion of acetyl group from the lysine residue of core histone and other protein that regulaes cellular function like proliferations, migrations, differentiation & cell apoptosis.

5. Subhasish Tapadar et al (2009); have reported Isoxazole moiety in the linker region of HDAC inhibitors adjacent to the Zn-chelating group: Effects on HDAC biology and antiproliferative activity.\(^\text{85}\)
Hydroxamic acid dependent histone deacetylase inhibitors containing an isoxazole moiety (5) nearby to the Zn$^{2+}$-chelating hydroxamic acid showed nano molar activity in the HDAC inhibitory assay and showed micro molar inhibitory activity against five pancreatic cancer cell lines. A series of hydroxamic acid depending on HDAC inhibitor where the isoxazole moiety was fixed in linker region and directly binded to the Zn$^{2+}$-chelating hydroxamic acid molecule has reported. The present results suggest that no important isozyme activity is gained by means of the more unbending isoxazole hydroxamate Zn$^{2+}$ binding group.

6. Chittari Pabba et al (2011); reported aryl ether and sulfone hydroxamic acids as potent Histone deacetylase (HDAC) inhibitors.$^{76}$

Sulfone and aryl ether based TSA analogs (6) was synthesized, and evaluated their inhibitory effect on HDACs. The potency depends on the substitution pattern on the arene ring was also observed. The multifold increase in activity with the replacement of large arylsulfone group with the corresponding aryl ether has shown. SAR results with the 6 are consistent with the hypothesis that these HDAC inhibitors operate as mimetics of the natural product TSA. These small molecule 6 may be useful as tools for biological research and as orally bio available anticancer drugs.

7. Eunhyun Choi et al (2011); reported Structure and property based design, synthesis and biological evaluation of $\gamma$-lactam based HDAC inhibitors.$^{77}$
Depending on the S.A.R. study and group optimization study of five-membered γ-lactam core containing δ-lactam HDAC inhibitors 7 were synthesized. Compounds 7 has decreased ring size and results in good binding in thin tunnel of target site. Phenyl, naphthyl & thiophenyl groups were introduce as the cap group. Lipophilic and heavy cap group increases strength of HDAC inhibition with the help of good lipophilic interaction between HDACs and inhibitor. The analogues with longer chain size are more active than shorter chain. The way to discover a powerful compounds *in vivo* experiment and optimization process for orally active applicants are in pipeline.

8. Xi Li et al (2012); reported molecular docking studies of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-phenyl acrylamide derivatives as inhibitors of HDAC activity. \(^{78}\)

3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-phenyl acrylamide derivatives (8) for the antitumor activities has reported. The compounds exhibited strong antiproliferative activities against HTC116 and HDAC inhibitory activities. Results showed that compound 8 has the potential to be developed for antiproliferative agents against HCT116. Docking simulation was performed to position into
the human HDAC-2 active site to determine the probable binding model. Western-blot results have also showed the series was a potential antitumor agent.


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Activities of N-aryl salicylamides with a hydroxamic acid moiety at 5-position against EGFR kinase and HDACs were evaluated efficiently by MTT method against human cancer cell lines A431, A549 and HL-60. Compounds showed the most potent inhibitory activity against A431 and A549. Compounds exhibited higher potency against HL-60 than gefitinib and SAHA. N-Aryl salicylamides with a hydroxamic acid moiety at 5-position is another new HDAC–EGFR dual inhibitors.

10. Yanshen Guo et al (2015); reported a binding modes of indole amide analogue as strong HDAC inhibitor and 3DQSAR analysis.  

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Docking simulation and three-dimension quantitative structures–activity relationship (3D-QSAR) analysis was conducted on series of indoles and amide analogue as strong histone deacetylase inhibitor. The study includes comparative molecule field analysis and comparative molecule similarity indice analysis. Selected ligand was docked into the main sites of human HDAC 1. Depending on the docking result, binding mode of indoles and amide analogue in the
human HDAC 1 positive charge core was presented. The indoles and amide groups were located in pocket, stitched to the proteins through a pair of hydrogen bonds with Asp99 Oxygen atom and amide NH group on ligand.

11. Hong Su et al (2008) has reported novel compounds with conjugated structure as anti-tumor agents specific HDAC-1 inhibitors.\textsuperscript{81}

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A series of hydroxamic acids with stereo defined-conjugated structures showed significant effect on noticeable cell cycle evolution. Most of compounds could persuade apoptosis. However, the selectivity and the inhibitory strength of these compound beside mammalian HDAC 1 and HDAC 4. The comparatively powerful compounds are the commercially available as a kit BIOMOL shown very compelling IC50. The general inhibitory activity of compounds in opposition to HDACs is acceptable. The relative pathetic inhibitory activities of compounds were also observed, due to the adverse joining of the stereo defined structures with enzyme catalytic pocket. It was also reported that the evaluation between the structure of oxamflatin and synthesized compound, accomplished that the profile of the stereo defined structure is very important in HDACs inhibition. Alignment independent GRINDs 3D-QSAR and docking studies on APHA carried out on homology modeling of maize HD1-A and HD1-B, revealed that in general a twisted molecular shape is a precondition for HD1-A selective inhibitory activity, while directly shape molecular skeleton leads to selective HD1-B compound. Thus, the profile of the stereo defined structure was also vital in sub type selectivity.

12. Takayoshi Suzuki et al (2005); has reported non hydroxamate histone deacetylase inhibitors as identification of a selective histone acetylating agents.\textsuperscript{82}
A series of SAHA-based non hydroxamate compounds (12) as (i) analogues bearing functional groups expected to chelate zinc ion bidentately or monodentately (ii) irreversible inhibition-oriented compounds and (iii) 14 Å internal cavity-targeting compounds and evaluated their inhibitory effect on HDACs has reported. Among them, methyl sulfoxide 15 inhibited HDACs in enzyme assays and showed great HDAC/TDAC selectivity in cellular assays. In conclusion, they identified a novel lead compound, from which potent HDAC isozyme-selective inhibitors can be developed. The findings of this study should also gave the way for the development of new medicines without side effects caused by interference with microtubule dynamics associated with HDAC6.

13. Chihiro Shi et al (2005); Cyclic amide/imide-bearing hydroxamic acid derivatives as class-selective histone deacetylase (HDAC) inhibitors. 83

Various structural types of cyclic amide/imide HDAC inhibitors (13), shows characteristic HDAC inhibition has observed selectively. SAR study of 13 reveals for selective HDAC inhibitory activity, linker chain with cap group is necessary. Further chemical alteration studies depended on SAR should give even more potent and more selective HDAC inhibitors. Compounds of 13 are potent HDAC inhibitors, effectual at the cellular level, so 13 are useful not only as discriminating tools to examine the function(s) of apiece HDAC class, but also as lead
compounds for the treatment of HDAC related diseases, which include cancer, cranial nerve
disease, immune disorders.

14. K. Vanommeslaeghe et al (2005); has reported DFT (destiny function theory) - depended ranking
of Zn$^{2+}$ binding groups in histone deacetylase inhibitors.$^{84}$

Histone deacetylase (HDACs) have recently attracted considerable interest as targets in the
treatment of cell proliferative diseases such as cancer. A general framework was proposed for
chemical groups that bind into the HDAC catalytic core. Based on this framework, a series of
groups was selected for further investigation. A method was developed to rank the HDAC
inhibitory potential of these moieties at the B3LYP/6-31G level, making use of extra diffuse
functions and of the PCM solvation model where appropriate. The resulting binding geometries
indicate that very stringent constraints should be satisfied in order to have bidental zinc
chelation, and even more so to have a strong binding affinity, which makes it difficult to predict
the binding mode and affinity of such zinc-binding groups. The chemical hardness and the pKa
were identified as important criteria for the binding affinity. Also, the hydrophilicity may have a
direct influence on the binding affinity. The calculated binding energies were qualitatively
validated with experimental results from the literature, and were shown to be meaningful for the
purpose of ranking.

15. Arkadii Vaisburg et al (2007); has reported N-(2-Amino-phenyl)-4(heteroarylmethyl)benzamides
(15) as new histone deacetylase inhibitors.$^{85}$
A range of N-(2-amino-phenyl)-4-(heteroarylmethyl)-benzamide (15) was designed and synthesized. These compounds were shown to inhibit recombinant human HDAC1 with IC50 values in the sub micromolar range. In human cancer cells growing in culture these compounds induced hyper acetylation of histones, induced the expression of the tumor suppressor protein p21 and inhibited cellular proliferation.

16. Xian ran He et al (2012); has reported phthalimide type Histone deacetylase inhibitors.

Several hydroxamic acid derivatives with a substituted phthalimide group (16) as a linker and/or cap structure, prepared during structural development studies based on thalidomide, were found to have histone deacetylase (HDAC) inhibitory activity. Structure–activity relationship study indicates main three important scaffold in the structure for better HDAC inhibitory activity. 1) Nature of the substituent introduced at the phthalimide nitrogen atom 2) Introduction of a hydroxamic acid structure 3) Distance between the N-hydroxyl group and the cap structure.
17. David J. Witter et al (2007); has reported benzo[b]thiophene-based histone deacetylase inhibitors.\textsuperscript{87}

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Novel benzo[b]thiophene HDAC inhibitors (17) are identified by high potency in HDAC and cellular proliferation assays. Substitution on fifth and sixth carbon molecules of benzo thiophene, found more active in cell proliferation inhibition. Moreover, all three structural series phenyl acetamide, benzylamine and benzoilamine were found to exhibit the same SAR with regard to the distance between the terminal aromatic moiety and the benzo thiophene core. Linker with 3 atom proved to be optimal for HDAC1 activity and homology models revealed a favorable interaction for the C6 substitution pattern and linker length.

18. Sampath kumar Anandan et al (2007); has reported thiazole 5-hydroxamic acids as novel histone deacetylase inhibitors.\textsuperscript{88}

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Novel series of substituted thiazole 5 hydroxamic acid (18) as HDAC inhibitors having both enzymatic and antiproliferative activity was designed very promptly. The sulfonamide analog
was found to have both enzyme and cell potency similar to SAHA. SAR study involved in the identification and necessity of substitution on various position of thiazoles. These analogues are most stable chemically. Thiazole ring worked as a linker between cap group and binding region.

19. Sylvie Fréchette et al (2008); has reported 4-(heteroarylanomethyl)-N-(2-aminophenyl)-benzamides and their analogs as a novel class of histone deacetylase inhibitors.\textsuperscript{89}

A novel class of HDAC inhibitors, the 4 (heteroarylanomethyl)-N-(2-aminophenyl)-benzamides (19) and their analogues was synthesized, which exhibited \textit{in vitro} anti-proliferative activities in numerous human cancer cells with little or no activity on normal cells, induced p21 expression and induced hyper acetylation of core histones. Cell cycle arrest of human cancer cells in a dose-dependent manner was also observed. These compounds have attractive in vitro profiles and show significant anti-tumor activity \textit{in vivo} in several human cancer xenograft model models. These results represent a significant step towards the development of small molecule HDAC inhibitors with favorable pharmaceutical properties.
20. Ester Muraglia et al (2008); has reported 2-trifluoro acetyl thiophene oxadiazoles as potent and selective class II human histone deacetylase inhibitors.\textsuperscript{90}

![Image of 2-trifluoro acetyl thiophene oxadiazoles](image.png)

Author has observed substitution of the carboxamide moiety of trifluoro acetyl thiophene carboxamides (20) gives potent and selective HDAC4 inhibitors. SAR described substitution at bio isosteric pentatomic hetero aromatic 1,2,4-oxadiazole, 1,3,4-oxadiazole and 1,3-thiazole led to the discovery of 1,2,4-oxadiazole derivatives as potent HDAC4 inhibitors. Some of the oxadiazole inhibitors displayed significant stability in the presence of HCT116 cells and oxadiazole 20 demonstrated good inhibition of class II HDAC, HDAC6, in cells. These compounds represent an important tool to elucidate the role and possible therapeutic implications of HDAC4 as a target in cancer therapy.

21. Mohsin M. Kamel et al (2010); reported sulfamides as novel histone deacetylase inhibitors.\textsuperscript{91}

![Image of sulfamides](image.png)

Authors have identified the sulfamide moiety (21) for design of novel HDAC inhibitors in accordance with role of HDAC in the cell and some enzymatic activity. Moreover selectivity of these inhibitors highly depends on the substitution on linker site and also depends on the size of the linker. The lysine-based inhibitors were HDAC1 and HDAC6 active, while the long-chain compounds were selective toward HDAC6.
22. Haishan Wang et al (2009); has reported N-Hydroxy-1,2-disubstituted-1H-benzimidazol-5-yl acrylamides as novel histone deacetylase inhibitors.\(^{92}\)

![Structure 22](image)

A series of N-hydroxy-1,2-disubstituted-1H-benzimidazol-5-yl acrylamides (22) were designed and synthesized as novel HDAC inhibitors. General SAR has been established for the substitutions at positions 1 and 2, as well as the importance of the ethylene group and its attachment to position 5. Authors have also shown the importance of hetero group in the inhibitory activity of HDAC.

23. Jiyoung Mun et al (2012); has reported Benzothiazole containing hydroxamic acids as histone deacetylase inhibitors and antitumor agents.\(^{93}\)

![Structure 23](image)

Author had identified diphenyl methylene hydroxamic acids as a new class of selective class IIa HDAC inhibitors. The original hit, N-hydroxy-2,2-diphenylacetamide (23) had class IIa HDAC activity in the sub micromolar range. While the rigidified oxygen analogue, N-hydroxy-9H-
xanthene-9-carboxamide is slightly more selective for HDAC7 with an \(I_{c50}\) of 0.05 \(\text{mM}\). Substitution of 6\(^{th}\) position is tolerated and allows for the modulation of selectivity amongst the HDAC class IIa isotopes. These inhibitors demonstrated cellular HDAC class II inhibitory activity in accordance with their enzymatic potencies.

24. Dao Thi Kim Oanh et al (2011); has reported Benzothiazole-containing hydroxamic acids as histone deacetylase Inhibitors and Antitumor Agents.\(^{94}\)

From the crystal structure of HDAC8 in complex with SAHA13 authors have noted that the phenyl ring of SAHA does not have significant interaction with HDAC8 enzyme. In their modeling study they also observed that the benzothiazol moiety has only minor interaction with the enzyme. The docking results obtained hitherto could not satisfactorily explain how the different 6-substituents affect the enzyme binding, though, as noted above, the larger substituents (–OC\(_2\)H\(_5\) and – SO\(_2\)CH\(_3\)) seemed to negatively affect the binding affinity. Nevertheless, this docking study does indicate that compounds with small substitution had high binding affinity for HDAC8 and it supports that inhibition of HDAC could be a prominent action mechanism for the cytotoxicity of these compound series, similar to SAHA.

25. Qiao Sun et al (2013); has reported novel histone deacetylase 1 inhibitors through click chemistry.\(^{95}\)
Author has developed one pot click chemistry approach to design a series of HDAC inhibitors, which show features of high potency and selectivity of HDAC1, as well as ability to inhibit several cancer cell growths. They identified a representative lead from this series, which was several folds more potent than SAHA against HDAC1. The compound showed promising in vitro anticancer activities against several cancer cell lines. Biological results demonstrate those compounds which demonstrated a high degree of HDAC1 inhibition also exhibited high levels of potency in the cell-based assay. In contrast, the weaker inhibitors of HDAC1 also generally exhibited reduced potency against cancer cells.

26. William Guerant (2015); has reported role of heterocyclic rings in target specific HDAC inhibitors.96

Author has classified HDAC inhibitors according to their key structure of scaffold. Like short chain fatty acids (butyrate and valproic acid), linear hydroxamic acids (SAHA and TSA), benzamides (MS-275), and cyclic peptides (FK-228 and CHAPs). According to class potency may also varied from mili molar to nano molar concentration. Author has also reported that HDAC inhibitors work differently from other chemotherapeutic agents. HDAC inhibitors (HDACi) have established great potential as in vitro anticancer agents through their ability to arrest the growth of nearly all distorted cell types, initiate differentiation, promote apoptosis, and inhibit angiogenesis. Treatment of cultured cancer cells with HDACi results in cell cycle arrest at G1 and G2 checkpoints at concentration of drug that also cause accretion of acetylated histones. Importantly, HDACi-induced toxicity is cancer specific, as doses that are toxic to transformed cells cause no apoptosis in normal cell lines.
27. Tao liu et al (2014); has reported Drug design and development of Histone deacetylase inhibitors for their medicinal applications in cancer chemotherapy.97

![Chemical Structure](image1)

Despite many advances in prevention and treatment of cancer, the ability to cure cancer is still in strong need to develop alternative and effective drugs. Conventional cancer chemotherapy is primarily inadequate due to the lack of selectivity for targeting cancer cells over their non-cancerous counterparts. Therefore, design and synthesis of novel potent, selective and less toxic anticancer agents remains one of the most pressing health problems. Histone deacetylase inhibitors (HDIs) are emerging as a new class of anticancer agents and have been shown to alter gene transcription. From the model of a crystallized human protein HDAC8, it is found that the amino acids involve in catalysis are located at the bottom of channels and covered with hydrophobic aromatic residues to interact with the inhibitor. Moreover, computational predictions suggested that some channel residues maintain flexibility to interact with HDAC1 inhibitors, particularly in linker region.

28. Madhusoodanan et al (2015); has published clinical study of various hidtone deacetylase inhibitors as a new target for cancer treatment.98

![Chemical Structure](image2)
Histone is a backbone of DNAs. Histone deacetylase is set of enzymes which removes acetyl group from the Histone and control the gene expression of tumor cells. They are widely used in so many body dysfunctions especially in cancer for target specific treatment by making various substitutions of different functional groups. HDAC inhibitors mainly interact the HDAC activity in cell cycle division like proliferation and differentiation process may led to apoptosis of tumor cells. As a result, HDAC inhibitor-based therapies have gained much attention for cancer treatment. To date, the FDA has approved three HDAC inhibitors for cutaneous/peripheral T-cell lymphoma and many more HDAC inhibitors are in different stages of clinical development for the treatment of hematological malignancies as well as solid tumors.