Hydroxamic acid — A novel molecule for anticancer therapy

Dilipkumar Pal, Supriyo Saha[1]

Department of Pharmaceutical Sciences, Division of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Guru GhasidashVishwavidyalaya (A Central University), Koni, Bilashpur, [1]Department of Pharmaceutical Chemistry, Himalayan Institute of Pharmacy and Research, Rajawala, Dehradun, India

J. Adv. Pharm. Tech. Res.

Abstract

Hydroxamic acid is a potent moiety not only in the field of cancer therapy but also as a mutagenic agent. Among the various derivatives of hydroxamic acid, SAHA (Suberoylanilide Hydroxamic Acid) is considered as a potent anticancer agent. Scientists from the different corner synthesized different hydroxamic acid moieties with some straight chain oxazole, thiadiazole, biphenyl moieties in the terminal position. Acetylation and deacetylation of histones of the core proteins of nucleosomes in chromatin play an important role in the regulation of gene expression. The level of acetylation of histones is established and maintained by two classes of enzymes, histone acetyltransferase and histone deacetylases, which have been identified as transcriptional coactivators and transcriptional corepressors, respectively. There is increasing evidence that aberrant histone acetylation has been linked to various malignant diseases. Great efforts are currently underway for the design of more potent and less toxic candidates for the treatment of cancer. In recent years, hydroxamic acid derivatives have attracted increasing attention for their potential as highly efficacious in combating various etiological factors associated with cancer. Our main intention to draw an attention is that this single functional moiety has not only fit in the receptor but also create a diversified activity.

Keywords: Cancer, histone deacetylase, hydroxamic acid, MMP inhibitor

INTRODUCTION

For the last four decades, a number of potential approaches have been proposed for the treatment of cancer. Several targets have already been identified in the process of novel anticancer therapy. One of the recent targets in which nowadays the scientists are showing their maximum interest is Histone Deacetylase (HDAC) enzyme. Great

Address for correspondence:
Dr. Dilipkumar Pal,
Associate Professor, Institute of Pharmaceutical Sciences,
Guru Ghasidash Vishwavidyalaya (A Central University),
Koni, Bilashpur, C.G – 495 009, India.
E-mail: drdilip2003@yahoo.co.in

efforts are currently underway for the design of more potent and less toxic candidates for the treatment of cancer. In recent years, hydroxamic acid derivatives have attracted increasing attention for their potential as highly efficacious in combating various etiological factors associated with cancer. Several attempts have already been made prior to synthesizing novel compounds irrespective of the targets; they are molecular modeling, molecular docking, QSAR studies, etc. Among them, molecular docking study was found to be a promising tool as compared with High Throughput Screening (HTS) in overcoming the limitations of unprecedented number of novel leads.

HISTONE DEACETYLASE STRUCTURAL FEATURES

HDAC enzyme was found to be one of the leading targets in the process of anticancer drug development. HDAC have been divided into three distinct structural classes as class (i/ii) zinc dependent and class (iii) as NAD (Nicotinamide adenine dinucleotide) dependent. These enzymes are a part of multiprotein complexes, catalyzing the removal of acetyl group from lysine residue on protein,

including histones. HDAC inhibitors have shown to bind the active site and block the substrate access, causing a resultant accumulation of acetylated histones. HDACIs (Histone deacetylase inhibitors) induce tumor growth inhibition, cell differentiation, and programmed cell death. HDACIs induce cancer cell cycle arrest, growth inhibition, differentiation, and programmed cell death. HDACI-induced cell cycle arrest and growth inhibition is usually correlated with transcriptional activation of p21WAF1/CIP1 (cyclin-dependent kinase inhibitor 1 or CDK-interacting protein), p27KIP1 (a cell-cycle regulatory protein that Interacts with cyclin-CDK2 and -CDK4, inhibiting cell cycle progression at G1), GADD45 (Growth Arrest and DNA Damage), inhibition of cyclin A, cyclin D, and thymidylate synthetase.[1]

HYDROXAMIC ACID AS ANTICANCER

Ragno *et al.* synthesized a new class of synthetic HDACIs, 3-(4-Aroyl-1-methyl- 1H-pyrrol-2-yl)-N-hydroxy-2-propenamides[2] which show minimal inhibitory concentration against HDAC in restricting the over expression of HDAC.
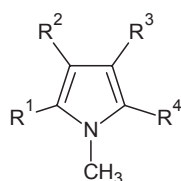
Kim *et al.* developed a new class of HDACIs, 3-(4-Substituted-phenyl)-N-hydroxy-2-propenamides by incorporating 1, 4-phenylene carboxamide as linker shows greater HDAC inhibition.[3]
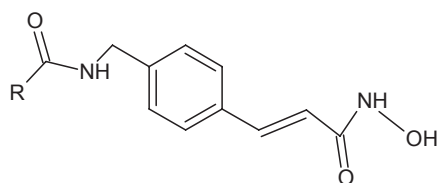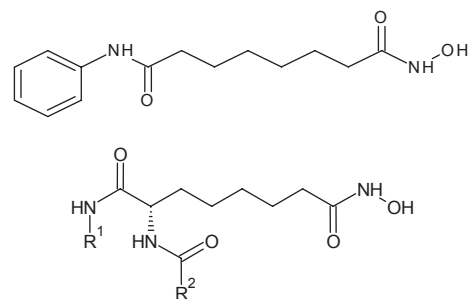
Lu *et al.* developed N-hydroxy-4-(4-phenylbutyryl-amino) benzamide,[4] a hydroxamate-tethered phenylbutyrate derivative with sub-micromolar potency in inhibiting HDAC activity and cancer cell proliferation.
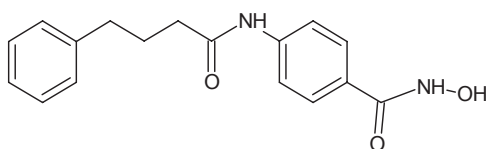
Belvedere *et al.* synthesized vorinostat-derived series of

substrate-based HDAC inhibitors and evaluated their inhibitory potential.[5]

Lee *et al.* synthesized and evaluated hydroxamic acid derivatives, bearing a 4-(3-pyridyl)phenyl group as a cap structure which exhibited potent HDAC inhibitory activity.[6]

Price *et al.*[7] investigated a series of thienyl-based hydroxamic acids[7] that include ADS100380 and ADS102550, which led to the identification of the 5-pyridin-2-yl-thiophene-2-hydroxamic acid, possessed modest HDAC inhibitory activity.
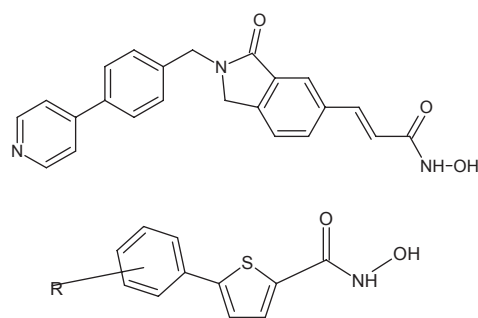
Hanessian *et al.* developed a series of ω-alkoxy ether by altering the chain length from six to eight of Suberoylanilide Hydroxamic Acid (SAHA).[8]
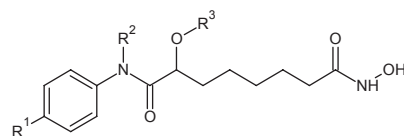
A series of structurally novel hydroxamic acid-based HDACIs were synthesized by Anandan *et al.*, where a zinc chelating group attached to a thiazole ring connecting the piperazine spacer and sulfonamide cap.[9]
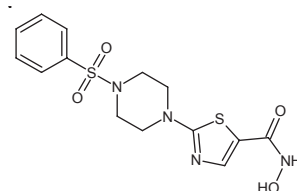
Dallavalle *et al.* designed, synthesized, and evaluated a series of hydroxamic acid-based histone deacetylase (HDAC) inhibitors characterized by a cinnamic spacer, capped with a substituted phenyl group.[10]
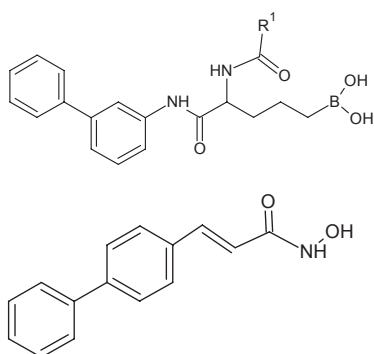
Suzuki *et al.* synthesized a series of boronic acid-based HDAC inhibitors, bearing an R-amino acid moiety which show some potent HDAC inhibitory activity.[11]

Charrier *et al.* synthesized and modeled new benzofuranone HDACIs that stimulate tumor suppressor gene expression as well as very effective in case of cancerous cell.[12]
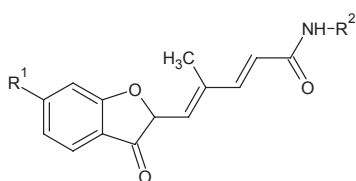
Koncic *et al.* examined few hydroxamic acid derivatives of nonsteroidal anti-inflammatory drugs and evaluated their antioxidant, radical scavenging activity with reference to BHA (Butylated Hydroxyanisole).[13]
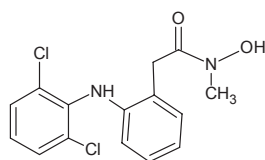
Lu *et al.* developed N-hydroxy-4-(4-phenylbutyryl-amino) benzamide, a hydroxamate-tethered phenylbutyrate derivative with sub-micromolar potency in inhibiting HDAC activity and cancer cell proliferation.[14]
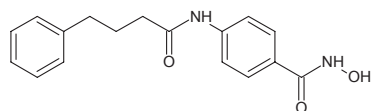
Zhou *et al.* designed and synthesized a N-(2-aminophenyl)-4-[(4-pyridin-3-ylpyrimidin-2-ylamino)methyl]benzamide[15]

which blocked cancer cell proliferation and induces histone acetylation.
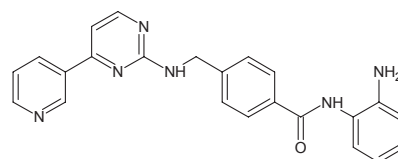
Pabba *et al.* developed a novel hydroxamic acid derivatives with aryl ether and aryl sulfone residues at the terminus of a substituted with unsaturated 5-carbon spacer moiety which showed greater HDAC inhibitory activity.[16]
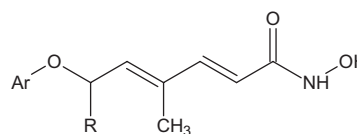
Angibaud *et al.* developed a series of pyrimidyl-5-hydroxamic acids which was prepared for evaluation as inhibitors of HDAC. Amino-2-pyrimidinyl can be used as a linker to provide HDAC inhibitors of good enzymatic potency.[17]
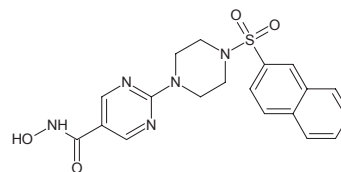
Codd *et al.* discovered SAHA (vorinostat, Zolinza®) and trichostatin A are inhibitors of the Zn(II)-dependent class I and class II HDACs resulting inhibition of Zn(II)-dependent HDACs that relaxes the chromatin structure and upregulates transcription.[18]
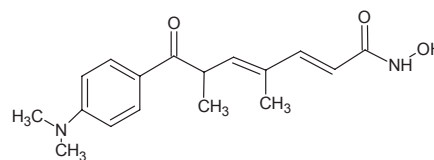
Trichostatin
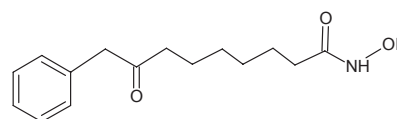
Suberoyl anilide hydroxamic acid

Gu *et al.* developed a new series of carbonyl and sulfur-containing analogs of SAHA as a potent inhibition of HDACIs.[19]

Sulfur containing SAHA derivative

Sulfur containing SAHA derivative

Rajak *et al.* developed two novel series of 2-[5-(4-substitutedphenyl)-[1,3,4]-oxadiazol/thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid[20] (tetrahydro-pyran-2-yloxy)-amides which were designed and synthesized as novel hydroxamic acid-based HDACIs.
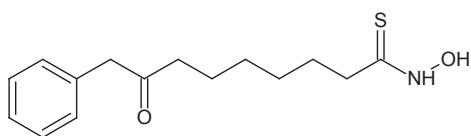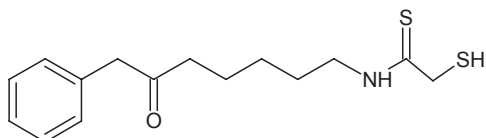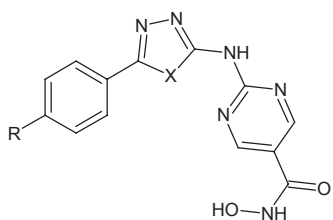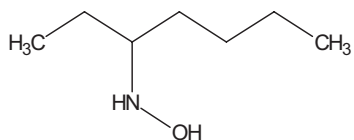

oxadiazole / thiadiazole derivative

Jiao *et al.* developed a novel series of N-hydroxy-4-(3-phenylpropanamido)benzamide derivatives comprising N-hydroxybenzamide group as zinc-chelating moiety which showed greater HDAC inhibitory activity.[21]


Mshvidobadze *et al.* synthesized various pyrazolo hydroxamic acid molecules which showed greater efficacy against cancer.[22]
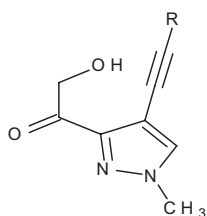
Shen *et al.* suggested that both the resistance of tumor cells to cisplatin and dose-related toxicity remain two of the most important problems in the chemotherapy of clinical oral squamous cell carcinoma. Cell viability and apoptotic assay were examined.[23]

Hrubec *et al.* described new linker-less HDAC inhibitors designed to exploit a unique sub-pocket in the HDAC8 active site which showed minimal concentration to inhibit apoptotic cells.[24]
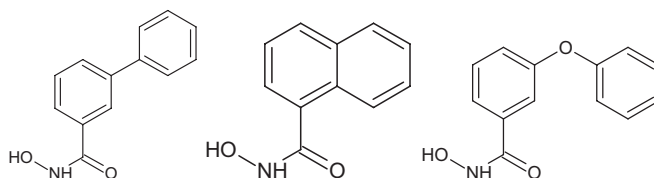
Various derivatives of hydroxamic acid molecule such as pyridyl hydroxamic acid, biphenyl hydroxamic acid, or the other substituted heterocyclic ring associated with hydroxamic acid has not only a great impact against HDAC but also human ovarian cancer, non-small cell lung cancer, and breast cancer cell line [Table 1].

HYDROXAMIC ACID AS MUTAGENIC AND MMP (MATRIX METALLOPROTEIN-ASE) INHIBITOR

Wang *et al.* evaluated the mutagenicity and antibacterial activity of a series of hydroxamic acids over a huge diversified range of bacterial strains. Among them, Salicylhydroxamic acid has shown antitubercular activity both *in vivo* and *in vitro*.[25]
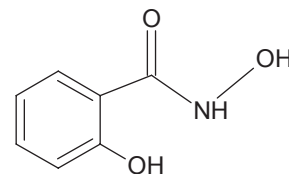
An *in vitro* antimicrobial evaluation was carried out by Davis *et al.* for cyclic hydroxamic acid and related lactams which showed the maximal antibacterial effects against *E. aerogenes* 13048, *S. marcescens* 13880, *K. pneumoniae* 10031, *P. aeruginosa* 10145, *E. coli* 9723, etc.[26]
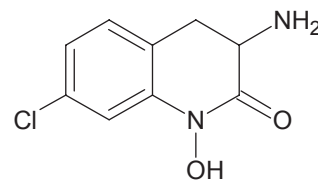
Brien *et al.* developed a complex with iron(III), copper(II), nickel(II), and zinc(II) complexes of salicylhydroxamic acid, anthranilic hydroxamic acid, and benzohydroxamic acid which showed some hydroxamate-peroxidase inhibitor interactions.[27]

Kokare *et al.* successfully used a novel reagent, phosphoric acid diethyl ester 2-phenyl-benzimidazol-1-yl ester,[28] that

Table 1: Different hydroxamic acid derivatives as HDAC inhibitor

| Compound structure	Research group	Target	IUPAC name	Reference
	Ragno R, Mai A, Massa S, Cerbara I, Valente S, Bottoni P, et al.	Restricted the over expression of HDAC.	3-(4-Aroyl-1-methyl- 1H-pyrrol-2-yl)-N-hydroxy-2 propenamide.	2
	Kim DK, Lee JY, Kim JS, Ryu JH, Choi JY, Lee JW, et al.	Showed greater HDAC inhibition.	3-(4-Substituted-phenyl)-N-hydroxy-2-propenamide.	3
	Lu Q, Wang DS, Chen CS, Hu YD, Chen CS	Sub micromolar potency in inhibiting HDAC activity and cancer cell proliferation.	N-hydroxy-4-(4-phenylbutyryl-amino) benzamide	4
	Belvedere S, Witter DJ, Yan J, Secrist JP, Richon V, Miller TA.	Cutaneous T-cell lymphoma	Amino suberoyl hydroxamic acid	5
	Lee S, Shinji C, Ogura K, ShimizuM, Maeda S, Sato M, et al	Exhibited potent histone deacetylase (HDAC) inhibitory activity.	4-(3-pyridyl)phenyl hydroxamic acid	6
	Price S, Bordogna W, Braganza R, Bull RJ, Dyke HJ, Gardan S, et al	Possessed modest HDAC inhibitory activity.	5-pyridin-2-yl-thiophene-2-hydroxamic acid	7
	Hanessian S, Auzzas L, Giannini G, Marzi M, Cabri W, Barbarino M, et al.	Human cell lines (NB4, H460, and HCT-116)	ω-Alkoxy analogues of SAHA	8
	Anandan SK, Ward JS, Brokx RD, Denny T, Bray MR, Patel DV, et al.	Breast cancer cell line MCF7	Thiazole-5-hydroxamic acids	9
	Dallavalle S, Cincinelli R, Nannei R, Merlini L, Morini G, Penco S, et al.	Human ovarian carcinoma IGROV-1 cells.	Biphenyl-4-yl-acrylohydroxamic acid	10
	Suzuki N, Suzuki T, Ota Y, Nakano T, Kurihara M, Okuda H, et al	HDAC inhibition.	Boronic acid base biphenyl hydroxamic acid.	11
	Charrier C, Clarhaut J, Gesson JP, Estiu G, Wiest O, Roche J, et al	NCI-H661 non-small cell lung cancer SEMA3F tumor suppressor genes.	Benzofuranone hydroxamic acid	12
	Lu Q, Wang DS, Chen CS, Hu YD, Chen CS	p21WAF/CIP1 over expression	N-hydroxy-4-[(4-phenylbutanoyl)amino] benzamide	14
	Zhou N, Moradei O, Raeppel S, Leit S, Frechette S, Gaudette F, et al	p21cip/waf1 protein expression, cell-cycle arrest, and apoptosis.	N-(2-aminophenyl)-4-{[(4-pyridin-3-ylpyrimidin-2-yl) amino]methyl}benzamide	15

Table 1: Continued

Compound structure	Research group	Target	IUPAC name	Reference
	Pabba C, Gregg BT, Kitchen DB, Chen ZJ, Judkins A.	Potent HDAC inhibitors with activities at low nanomolar levels	Aryl ether hydroxamic acid	16
	Angibaud P, Arts J, Emelen KV, Poncelet V, Pilatte I, Roux B, *et al*	P388 mouse leukemia	N-hydroxy-2-[4-(naphthalen-2-ylsulfonyl)piperazin-1-yl]pyrimidine-5-carboxamide	17
Trichostatin	Codd R, Braich N, Liu J, Soe CZ, Pakchung AAH	Zn(II)dependent class I and class II histone deacetylases	(2E,4E)-7-[4-(dimethylamino)phenyl]-N-hydroxy-4,6-dimethyl-7-oxohepta-2,4-dienamide	18
Sulfur containing SAHA derivative / Sulfur containing SAHA derivative	Gu W, Nusinzon I, Smith RD, Horvath CM, Silverman RB	Histone deacetylase inhibitors	N-hydroxy-8-oxo-9-phenylnonanethioamide N-(6-oxo-7-phenylheptyl)-2-sulfanylethanethioamide	19
oxadiazole / thiadiazole derivative	Rajak H, Agarawal A, Parmar P, Thakur BS, Veerasamy R, Sharma PC, *et al*	Histone deacetylase inhibitors	Oxazole / thiadiazole derivative of hydroxamic acid	20
	Jiao J, Fang H, Wang X, Guan P,Yuan Y, Xu W	Greater HDAC inhibitory activity	N-hydroxyheptan-3-amine	21
	Hrubec KK, Marshall BL, Hedglin M, Verdin E, Ulrich SM	Minimal concentration to inhibit apoptotic cells.	N-hydroxybiphenyl-3-carboxamide N-hydroxy-3-phenoxybenzamide N-hydroxynaphthalene-1-carboxamide	24

was designed and synthesized and its applicability was demonstrated for the preparation of O-alkyl hydroxamic acids. The O-alkyl hydroxamic acids of N-protected amino acids were also synthesized.

Reiter *et al*. used a series of sterically hindered sulfonamide hydroxamic acids which are the potent inhibitors of MMP-13. The metabolically more stable compounds in the series contain either a monocyclic or bicyclic pyran ring adjacent to the hydroxamate group.[29]
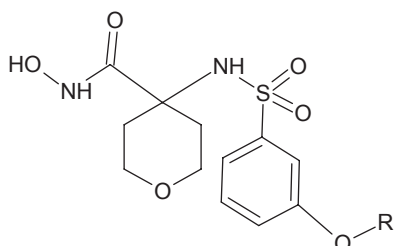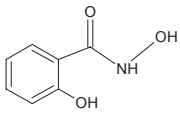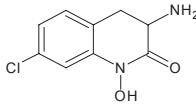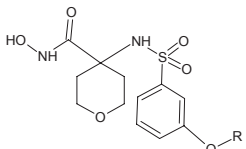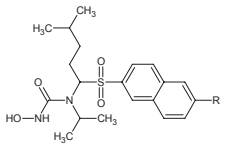
Tommasi *et al*. discovered a series of hydroxamic acid inhibitors of MMP-13 that do not significantly inhibit MMP-2 (gelatinase-1). MMP-2 has been implicated in the musculoskeletal side effects resulting from pan-MMP inhibition due to findings from spontaneously occurring human MMP-2 deletions.[30]
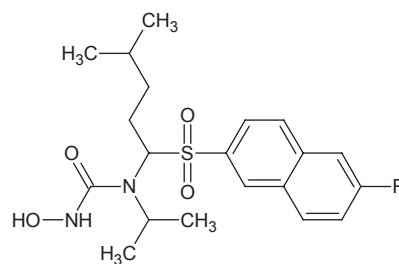
Sulfonamide hydroxamic acid molecule has a great influence against metalloproteinase enzyme and if that molecule was further substituted with naphthyl molecule, it also shows a greater affinity to that enzyme [Table 2].

Table 2: Different hydroxamic acid derivatives as mutagenic and MMP inhibitor

Compound structure	Research group	Target	IUPAC name	Reference
	Wang CY, Lee LH. A.	Mutagenic	N,2-dihydroxybenzamide	25
	Davis A, Hulme KL, Wilson GT, Mccord TJ.	Mutagenic and antimicrobial against E.aerogenes13048, S. marcescens13880, K. pneumoniae 10031 etc.	3-amino-7-chloro-1-hydroxy-3, 4-dihydroquinolin-2(1H)-one	26
	Reiter LA, Robinson RP, McClure KF, Jones CS, Reese MR, Mitchell PG.	Potent inhibitors of MMP-13	Sulfonamide hydroxamic acid derivative	29
	Tommasi RA, Weiler S, McQuire LW, Rogel O, Chambers M, Clark K, et al.	Inhibitor of MMP-13	Newer generation of naphthyl- sulfonamide hydroxamicacid derivative.	30

CONCLUSION

So, hydroxamic acid molecule has a greater impact in the field of pharmaceutical chemistry, though it has not only used as an anticancer but also for other mutagenic problems. From the total review, we can conclude that there was a diversified activity profile that occurred due to the changes in the various position of a molecule with the same hydroxamic acid group on the terminal. So, this single molecule can work further more and more with various other compatible groups and not only in the field of cancer therapy but also other associated diseases.

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