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Review Article

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RECENT SMALL MOLECULES WITH BIFUNCTIONAL HDAC THERAPEUTICS

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ABSTRACT

Histone deacetylases (HDACs) are studied as prime targets for a broad radius of neoplasm and other diseases, they are associated with the initiation, expansion and viability of tumor cells. However, the built-in diverseness and numerous genetic deformity of various diseases question the clinical utilization of these single target focussed drugs. To control the problems associated with single target perspective, a way out approach is to target HDACs and other relevant targets of the disease at the same time like Topoisomerase, Cyclin-dependent kinase, Heat shock protein, Janus kinase, VEGF, CYP51, EGFR, LSD1, BRD4, etc. with a single drug attracted a great deal of attention of in drug discovery and development process. New molecules were synthesized which incorporate the binding characteristics of both the targets. This review highlights the recent discovery and development of small molecules synthesized as dual inhibitors against HDACs and other related protein targets for the disease. Considerable studies were undertaken to discover molecule having duel HDAC inhibitory potential and thereby, various drugs have emerged from this attempt.

KEYWORDS: HDAC, duel inhibitors, Cell lines, structures, Topoisomerase.

INTRODUCTION

Drug design is the key process in discovery of advanced medicines by applying the knowledge and understanding of drug-receptor binding. Traditional drug-design concept apply the notion of 'single-target, single-drug, single-disease' in which designed molecules are modulated to bind with a single protein. Single protein target, leave out the complications of the cell and makes the validation drug targets uncertain.[1] So, concurrent assessment of two or multiple targets is unavoidable to target complex diseases like cancer. Novel approaches were employed to design duel receptor targetting molecules that bind with prespecified targets offer greater therapeutic benefits through intervention with multiple pathways and possible synergistic action. Moreover, targeting multi receptors can let down the possibility for developing drug resistance. The receptor choosing approch is often based on the clinical data, phenotypic screening of drug combinations, or in-silico approaches.

Histone deacetylases (HDACs), are class of "epigenetic enzymes" that have protein substrates that control the gene expression, proliferation and viability of cells. HDACs split acetyl groups, from N-Acetyl lysine, it act by removing acetyl groups from histones and other protein regulatory factors, with functional consequences on chromatin remodeling and gene expression profile.[2] HDAC inhibition causes the accumulation of acetylated forms of these proteins, altering their function. HDAC in association with other targets significantly helped in targeting various diseases. The promising therapeutic benefits associated with HDACs highlight the importance of identifying dual inhibitors of these enzymes. HDAC inhibitors are being explored for treating various diseases especially cancers, viral infections, inflammation, neurodegenerative diseases, and metabolic disorders.[3]

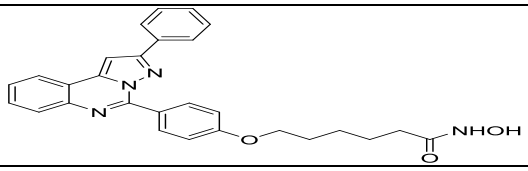
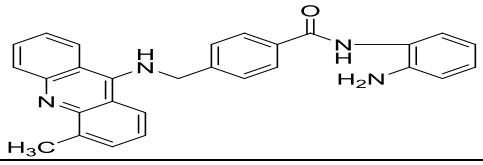
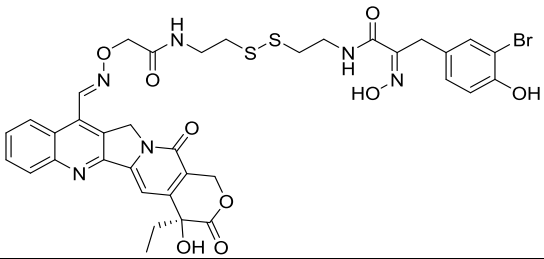
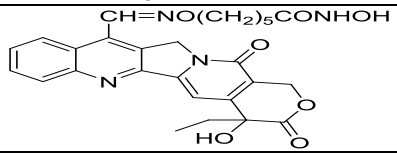
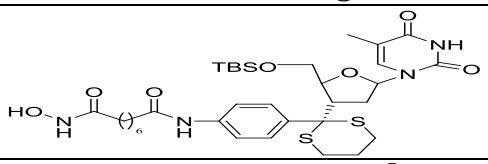
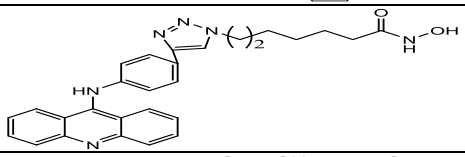
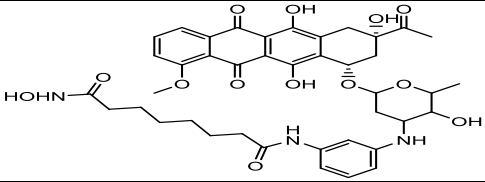
This review emphasizes on the current studies of small molecule inhibitors, which are potent duel inhibitors, which simultaneously inhibit the functions of HDACs and other specific targets for various cell lines.

HDAC/TOPOISOMERASE (Topo) duel inhibitor.

Pyrazolo quinazolines were designed and synthesised as duel inhibitors of topoisomerase I and HDAC1, synthesised compounds contributed to cellular oxidative stress and promoted apoptosis via a mitochondria-independent pathway and were non-DNA intercalator, having anticancer effect.[4] Similarly, 16 new N-(2-aminophenyl) benzamide acridine analogues were synthesized as duel Topo I and isoform-selective HDAC multifunctional inhibitors as anticancer agents. Compounds contain a benzamide pharmacophore (ZBG) which promote inhibition of class I HDAC.[5] A new

dual-acting multivalent hybrid molecule containing a camptothecin-psammaplin A scaffold showed a broad spectrum of antiproliferative activity, with IC50 values in the nanomolar range being synthesized. Camptothecins are clinically validated topoisomerase I (Top1) inhibitors whereas Psammaplin A in compound displays an intriguing structure, being a symmetrical disulfide with a cystamine linker functionalized on both sides by α-(hydroxyimino)acyl moieties. Studies showed that the disulfide bridge and the α hydroxyiminoamide moieties are necessary for HDAC inhibition.[6,7] A novel class of nucleoside- suberoylanilide hydroxamic acid (SAHA) derivatives having duel inhibitory activities toward HDAC and Topo II were synthesized, compounds exhibited antiproliferative activity toward cancer cell lines including MCF-7 (breast), HCT-116 (colon), and DU-145 (prostate) cancer cells at a low micromolar level.[8] Similarly, efforts were put into synthesizing a series of acridine hydroxamic acid derivatives, the compounds increase the accessibility of DNA by inducing DNA relaxation, facilitating Topo inhibitors binding with chromatin and thus potentiating the antitumor sensitivity of Topo inhibitors.[9] Dual-acting HDAC and Topoisomerase II inhibitors from SAHA and anthracycline daunorubicin as anticancer agents were synthesised, the introduction of the HDACi via N-benzylation of the DAU amino group would be compatible with Topo II inhibition and possibly engender the positive attributes of N-benzylated anthracyclines to the resulting conjugates with duel activity.[10]

Table 1: Structure and Cell line used for the study HDAC/Topo duel inhibitors.

Structure of Synthesised Compounds	Cell lines used for activity	Reference No
	A549, H1299, MCF-7, MDA-MB-231, HT-29	[4]
	CCRF-CEM, K562 and U937	[5]
	MINO, MAVER-2, JECO-1, U-2932, OCI-LY3, L-428, KM-H2, DG-75, NB4, NCI-H460, CAPAN 1, A431, HeLa, HT29, DU145, HepG2, A2780, A2780-Dox, MM432, MM473, MM487	[6]
	NCI-H460, CAPAN 1, A431, HeLa , HT29, DU145, HepG2 , A2780, A2780-Dx	[7]
	MCF-7 , HCT-116 and DU-145	[8]
	U937	[9]
	DU-145, SK-MES-1, MCF-7	[10]

HDAC/ Cyclin-dependent kinase (CDK) duel inhibitors

HDAC and CDK inhibitors have showed to synergistically suppress cancer cell proliferation and induce apoptosis. A series of novel indirubin derivatives were designed and synthesized. The synthesised compounds have remarkable CDK2/4/6 and HDAC6 inhibitory activity and efficiently induced apoptosis and S-phase arrest in several cancer cell lines to prevent the proliferation of a non-small-cell lung cancer cell line.[11] Similarly, a series of novel 1-H-pyrazole-3-carboxamide-based derivatives targeting HDAC and CDK were reported, compounds exhibited excellent antiproliferative activities against five solid cancer cell lines which was associated with increasing the intracellular reactive oxygen species (ROS) levels[12] A series of purin derivatives as HDAC/CDK dual inhibitors were synthesised as anticancer agents.[13] Similarly, a series of hydroxylamine or o-diaminoaniline as novel CDK4 inhibitors by incorporating the HDAC pharmacophores were synthesised. The enzymatic inhibitory (HDAC1, CDK2, CDK4, and CDK6) activities and cytotoxicities of these compounds were evaluated. HDAC isoforms inhibitory activity, cell cycle arrest assay, cell apoptosis analysis, cell migration, and cell colony formation assay were performed.[14]

HDAC/ Heat shock protein (Hsp 90) duel inhibitors

A new series of Hsp90/HDAC dual inhibitors as a new strategy for the development of antifungal therapeutics to combat azole-resistant candidiasis was reported. Compounds exhibited fungal-selective inhibitory effects on Hsp90/ HDACs, leading to low toxicity and excellent in vitro and in vivo synergistic antifungal potency to treat fluconazole-resistant candidiasis.[15] A series of N-alkyl-hydroxybenzoyl anilide hydroxamates as dual inhibitors of HDAC and Hsp 90 is reported which can modulate immunosuppressive ability of tumor area. Synthesised compounds, induce HSP70 expression and down regulate Hsp 90 client proteins, and displayed their HDAC inhibitory effects due to increased acetylated α-tubulin and histone H3 levels. The compound significantly reduce programmed death-ligand 1 (PD-L1) expression in IFN-γ treated lung H1975 cells in a dose dependent manner.[16] Another novel series was designed and synthesised as dual acing HDAC6 and Hsp90 inhibitors. Synthesised compounds were able to selectively provide an increased level of acetylation of αtubulin, while showing no effects on histone H3 acetylation. In vitro assay confirmed the synthesised compound of breast cancer cell proliferation.[17] New study recruited Indoline-based hydroxamate scaffolds with the ability to concomitantly modulate both targets (HDAC6 and HSP90). And was pinpointed in the present endeavor to attenuate blue light-induced cell migration and retinal neovascularization by inhibiting VEGF production.[18]

HDAC/ Janus kinase (JAK) duel inhibitors

A novel series of pyrimidin-2-aminopyrazol hydroxamate derivatives with concurrent inhibition of JAK and HDAC exhibited improved antiproliferative and proapoptotic activities over SAHA and ruxolitinib in several hematological cell lines and is used in the treatment of cancers. Most compound showed a balanced activities against both JAK2 and HDAC6 with half-maximal inhibitory concentration at the nanomolar level.[19] Similarly, a novel JAK2 and HDAC dual inhibitors as potent anti-proliferative activity toward acute myeloid leukemia (AML) models and synergized with fluconazole for the treatment of resistant C. albicans infections.[20] Anothere series, merged the core features of ruxolitinib a marketed JAK1/2 inhibitor, with the HDAC inhibitor vorinostat, leading to new molecules that are bispecific targeted JAK/HDAC inhibitors. Of all synthesised pyrazole substituted pyrrolopyrimidine derivatives as most potent and inhibits JAK1 and HDACs 1, 2, 3, 6, and 10 and is selective for the JAK family against a panel of 97 kinases and are used against hematological cell lines.[21] Another study showed pharmacophore merging strategy combining the JAK2/FLT3 inhibitor pacritnib with the vorinostat, to create bispecific single molecules with both JAK and HDAC targeted inhibition. A preferred ether hydroxamate inhibits JAK2 and HDAC6 with low nanomolar potency, against HDACs 2 and 10, submicromolar potent against HDACs 1, 8, and 11, and >50-fold selective for JAK2 in a panel of 97 kinases. The compound cause blockade in several hematological cell lines.[22] A series of pyrrolo[2,3-*d*]pyrimidine-based derivatives as potent JAK and HDAC dual inhibitors is discovered, compounds potently inhibited JAK1/2/3 and HDAC1/6 and displayed antiproliferative and proapoptotic activities in triple-negative breast cancer cell lines, also inhibited the tumor growth in MDA-MB-231 xenograft tumor model.[23] Similarly, a novel series of 2,4-dianilinopyrimidine derivatives is synthesised, which could simultaneously inhibit JAK2 and HDAC1. Among which, the most potent compound displayed balanced inhibitory activity against HDAC1and JAK2, also demonstrated good antiproliferative activity against tested various cancer cell lines.[24]

HDAC/ vascular endothelial growth factor (VEGF) duel inhibitors.

A series of hybrids bearing *N*-phenylquinazolin-4-amine and hydroxamic acid moieties were designed and identified as dual VEGFR-2/HDAC inhibitors. Most potent compound exhibited inhibitory activity against HDAC and VEGFR-2 and is active against a human breast cancer cell line MCF-7. Docking simulation supported the initial pharmacophoric hypothesis and suggested a common mode of interaction at the active binding sites of VEGFR-2 and HDLP.[25]

HDAC/ Epidermal growth factor receptor EGFR duel inhibitors.

A novel series of *N*-aryl salicylamides with a hydroxamic acid moiety at 5-position was synthesised. All compounds displayed inhibitory activity against EGFR and HDACs and showed good antiproliferative

activitiy by MTT method against human cancer cell lines A431, A549 and HL-60.[26]

HDAC/BRD4 duel inhibitors.

A series of indole derivatives as duel HDAC and BRD4 inhibitors. In vitro anti-proliferation activities showed the potent inhibition of HDAC3 and BRD4. It was confirmed that the lead compound could up-regulate the expression of Ac-H3 and reduce the expression of c-Myc by western blot analysis.[27] Similaly, compounds were synthesised by combining bromodomain and HDAC inhibitory activity in one molecule. The representative inhibitor, showed potent antiproliferative activities against human leukemia cell line K562 and MV4-11 in cellular assays.[28]

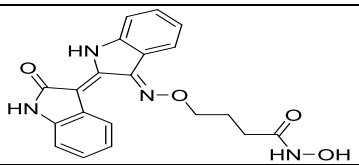
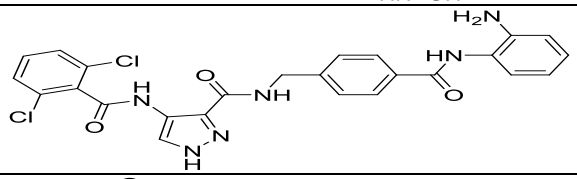
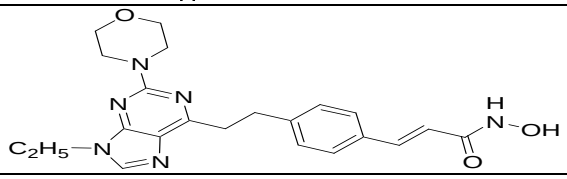
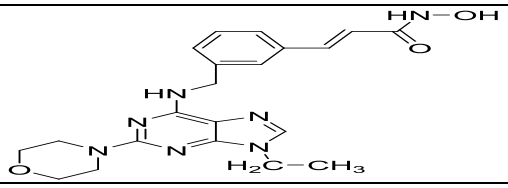
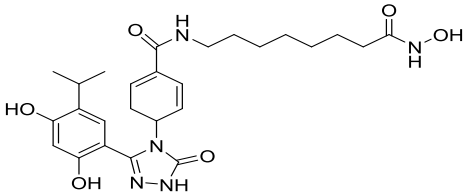
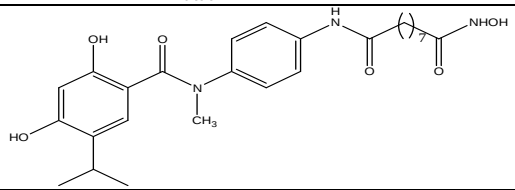
HDAC/CYP51 duel inhibitors.

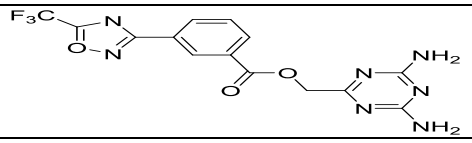
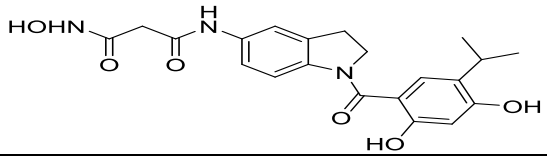
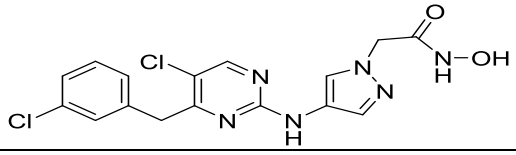
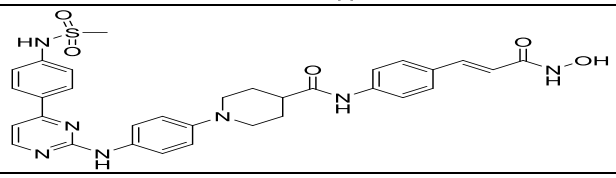
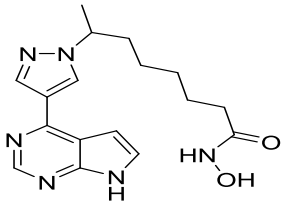
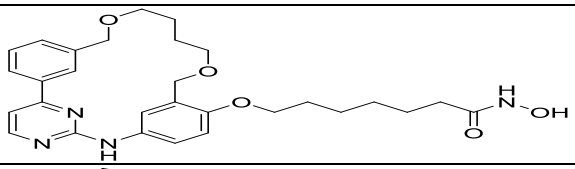
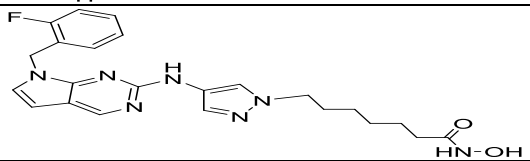
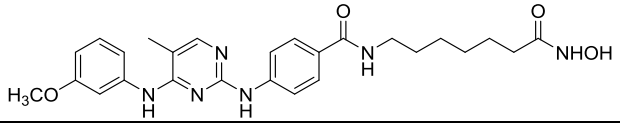
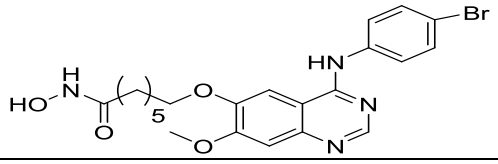
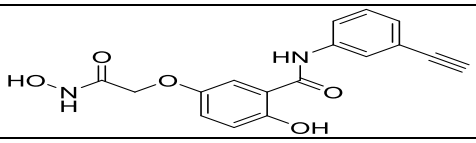
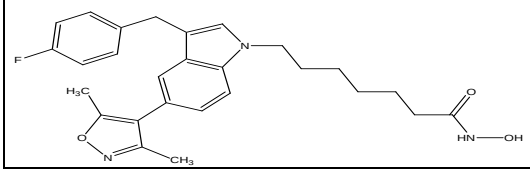
New series of CYP51/HDAC dual inhibitors containing the piperazine linker were designed and synthesized as a novel broad-spectrum antifungal agents, compounds showed potent *in vitro* and *in vivo* antifungal activity against *C. neoformans* and *C. tropicalis* infections and down-regulating resistance-associated genes. Study highlighted the CYP51/HDAC dual inhibitors.[29] Similarly first generation of lanosterol 14αdemethylase (CYP51)-histone deacetylase (HDAC) dual inhibitors, which exhibited potent antifungal activity against azole-resistant clinical isolates for treatment of invasive fungal infections, particularly candidiasis. Lead compound were highly active both in vitro and in vivo to treat azole-resistant candidiasis. Antifungal mechanism studies revealed that they acted by blocking ergosterol biosynthesis and HDAC catalytic activity in fungus, suppressing the function of efflux pump, yeast-to-hypha morphological transition, and biofilm formation.[30]

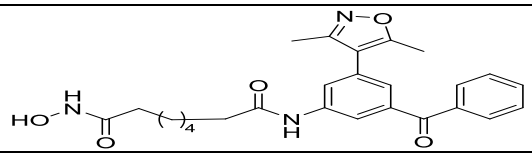
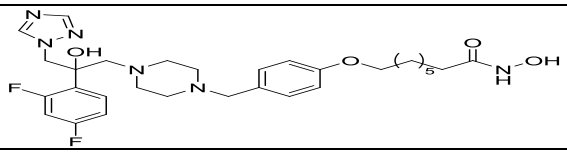
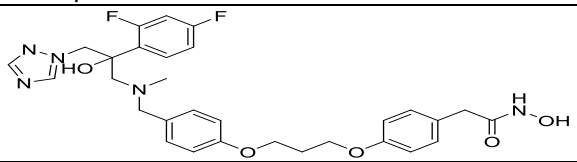
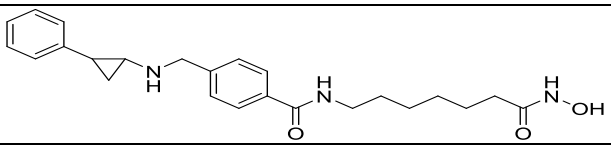
HDAC/LSD1 duel inhibitors.

Similarly, series of tranylcypromine derivatives as novel LSD1/HDACs dual inhibitors having strong antiproliferative activity were synthesised, the compounds displayed inhibitory activity against HDAC1, HDAC2 and LSD1 and showed activity against MGC-803, MCF-7, SW-620 and A-549 human cancer cell lines.[31]

Table 2: Structure and Cell line used for the study of Duel Inhibitors.

Structure of Synthesised Compounds	Activity/Cell line	Reference
HDAC/CDK duel inhibitors		
	A549	[11]
	A375, HCT116, H460, Hela cells	[12]
	A549, HepG2, CAL-148	[13]
	H460, MDA-MB-468, HCT116, and HepG2	[14]
	Antifungal agent azole-resistant candidiasis	[15]
	A549, HCT116, H1975	[16]

	MCF7	[17]
	ARPE-19	[18]
	HEL, K562, MOLT4, Jurkat	[19]
	HEL60, K562, HEL, Antifungal agent	[20]
	HL-60, HEL92.1.7, Jurkat, TAMH, AC10, KMS-12-BM, OPM-2, XG-6, KG-1, MOLM-14, MV4-11, NKYS, KHYG, MDA-MB-231, MCF7, HCT-116, PC3	[21]
	MDA-MB-231, HCT-116, PC-3, MCF-7 HL-60, HEL92.1.7, Jurkat KMS-12- BM, OPM-2, KG-1, MOLM-14, NKYS, KHYG	[22]
	MDA-MB-231	[23]
	A549, HepG-2, MDA-MB-231 and Jurkat	[24]
HDAC/VGFER duel inhibitors		
	MCF-7	[25]
HDAC/EGFER duel inhibitors		
	A431, A549 and HL-60	[26]
HDAC/BRD4 duel inhibitors		
	THP-1	[27]

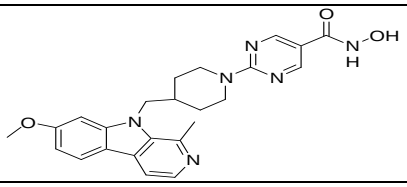
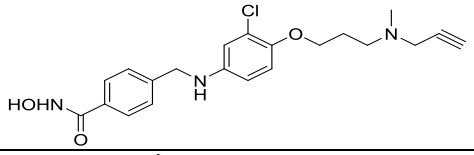
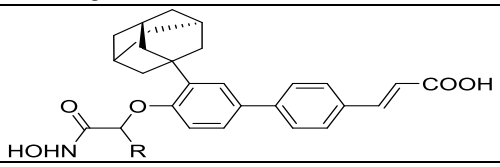
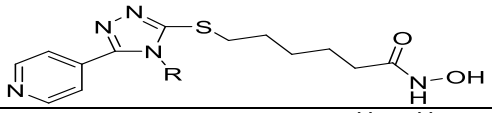
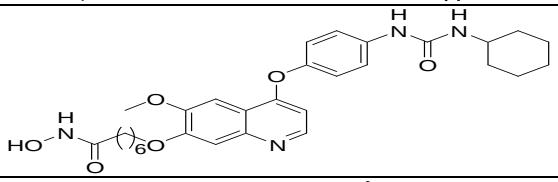
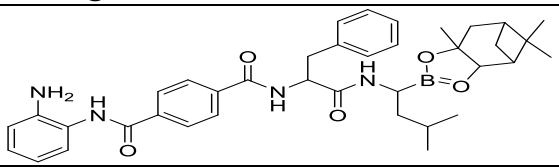
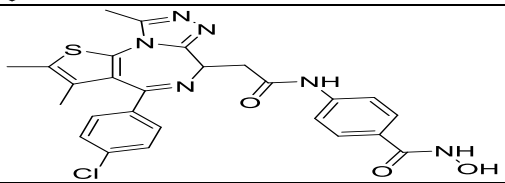
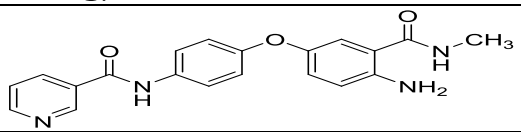
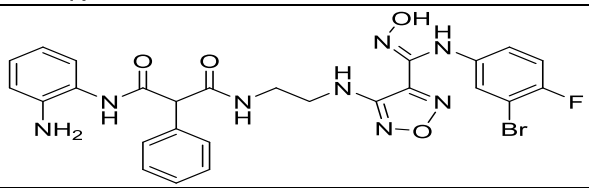
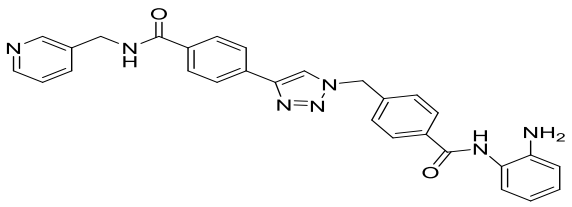
	K562, MV4-11	[28]
HDAC/CYP51 duel inhibitors.		
	Antifungal agent SC5314, 0304103, 7781, 4108, 10061, 9770	[29]
	Antifungal agent- C5314, 0304103, 7781, 4108, 5008, H99	[30]
HDAC/LSD1 duel inhibitors.		
	MGC-803, MCF-7, SW-620 and A-549	[31]

HDAC with other targets

Other than these targets, HDAC showed synergistic action with many other targets. A series of harmine base compounds synthesized showed duel inhibition of HDAC 1 and 6 and DNA target, is reported by to cause DNA damage by intercalating DNA for treating solid tumor. The most potential compound could be able to bind with DNA to cause DNA damage which in turn caused cells apoptosis through p53 signaling pathway. The compounds exhibited significant anti-proliferation effects and displayed low toxicity in normal cells.[32] Another series of N-methylpropargylamine-conjugated hydroxamic acids were synthesized and evaluated as dual inhibitors of Mono amine oxidase (MAO) and HDAC for Glioma treatment. Compounds displayed potent MAO A inhibition and inhibit HDAC isoforms and cell growth in the micromolar to nanomolar IC50 range. These selective inhibitors increase histone H3 and α-tubulin acetylation and induce cell death via nonapoptotic mechanisms.[33] Similarly, hybrid molecules to target DNA polymerase α (POLA1) and HDACs simultaneously were synthesised. Synthesised molecule showed antiproliferative activity at nanomolar concentrations on human solid and hematological cancer cell lines. In vitro functional assays confirmed that these molecules inhibited POLA1 primer extension activity, as well as HDAC11, by inducing acetylation of p53, activation of p21, G1/S cell cycle arrest, and apoptosis. Antitumor activity was also confirmed in in-vivo models.[34] Dual inhibitors, 5-pyridinyl-1,2,4-triazoles of HDAC2 and focal adhesion kinase (FAK) was designed and synthesized, most potent compound was found to be superior to reference drugs vorinostat and valproic acid in its ability to inhibit growth/proliferation of A-498 and Caki-1 renal cancer cells. Findings suggested the lead compound a promising dual-acting HDAC2/FAK inhibitor.[35] Three new series of 4-phenoxyquinoline derivatives as urea, semicarbazone and amido urea as c-Met/HDAC bifunctional inhibitors by merging pharmacophores of c-Met and HDAC inhibitors were synthesised. Compound showed efficient antiproliferative activities against both MCF-7 and A549 cells with greater potency than the reference drug SAHA and Cabozantinib. The designed c-Met/HDAC dual inhibitors composed of the 4-phenoxyquinoline skeleton with a hydroxamate group which is essential for chelation with the zinc ion in the active site of HDAC. The potent lead compound showed anti-proliferative activity in the low micromolar range on two human cancer cell lines MCF-7 and A549.[36] Duel inhibitors targeting both HDACs and proteasomes to address the resistance of bortezomib were synthesised. Synthesised compounds showed excellent inhibition against proteasome and good selectivity against HDACs and exhibited potent antiproliferative activities against the bortezomib-resistant cell line, (1:1).[37] Similarly, a new, effective therapeutic strategy and the design of small-molecule inhibitors that simultaneously target bromodomain and extra-terminal (BET) and HDAC, potentially serving as promising therapeutic agents for pancreatic cancer was reported.[38] A series of novel phenoxybenzamide analogues with inhibition of Raf and HDAC was designed and synthesised. HDAC inhibitors act synergistically with kinase inhibitors for the treatment of cancer. The lead compound showed potent antiproliferative activities against Hepg2 and MDA-MB-468 in cellular assays.[39] First generation of dual indoleamine 2,3-dioxygenase 1 (IDO1) and HDAC inhibitors were synthesised, lead dual inhibitor showed excellent and balanced activity against both IDO1 and HDAC1, whose dual targeting mechanisms were validated in cancer cells. Compound had good pharmacokinetic profiles as an orally active antitumor agent and significantly reduced the l-kynurenine level in plasma. In particular, it showed excellent *in vivo* antitumor efficacy in the murine LLC tumor model

with low toxicity.[40] Similarly a series of compounds were designed and synthesised compounds which simultaneously inhibit nicotinamide phosphoribosyltransferase (NAMPT) and HDAC, showed excellent in vivo antitumor efficacy in the HCT116 xenograft model.[41]

Table 3- Structure, Other Target receptors and Cell line used for the study.

Structure	Target Receptors	Activity/Cell line	Ref. No
	Duel HDAC and DNA targetting duel inhibitors.	HCT-116	[32]
	Duel HDAC and MAO inhibitors.	Glioma cells	[33]
	Duel HDAC and POLA 1 inhibitors.	H460, MM473, MM487	[34]
	Duel HDAC and FAK duel inhibitors	HCT116, HT-29, K562, KG-1, A-498, Caki-1	[35]
	Duel HDAC and c-Met duel inhibitors.	MCF-7, A549	[36]
	Duel HDAC and Proteasomes duel inhibitors	RPMI-8226, U266, KM3,KM3/BTZ, HUVEC, GES-1, HL-7702, Het-1A	[37]
	Duel HDAC and BET duel inhibitors	Pancreatic cancer- Capan-1 tumor xenograft model	[38]
	Duel HDAC and Raf duel inhibitors.	K562, MV4-11, Hepg2, MDA-MB-468	[39]
	HDAC and IOD1 duel inhibitors	IDO-1, LLC, CT-26, A549, HCT-116, HT-29	[40]
	HDAC/NAM T duel inhibitors.	HCT116, MDA-MB-231, HepG2	[41]

CONCLUSION

HDAC inhibitor is a group of drugs, particularly in fusion with other inhibitors are used for treatment of several types of malignancies. Small molecules with duel HDAC inhibitory action showed activity against various cancer cell lines and received regulatory acceptance for chemotherapy and are is in clinical development for oncology as well as alternative therapeutic indications. However a number of drugs have been developed with a single protein target, overlooks the complexity of the cell and makes the process of validating drug targets uncertain. To overcome the limitations of a single target approach, simultaneously targeting HDACs and other relevant targets of the disease like Topoisomerase, Cyclin-dependent kinase, Heat shock protein, Janus kinase, vascular endothelial growth factor, Epidermal growth factor receptor, BRD4, CYP51, LSD1 etc. with a single molecule has been recently employed and attracted much attention of medicinal chemists in drug discovery. Total 49 such small molecules having duel HDAC inhibitory action with other receptors were studied and showed a promising future prospective for cancer and other ailments.

CONFLICT OF INTEREST

There is no conflict of interest.

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