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Unraveling the Role of HDAC Inhibitors in Targeted Cancer Therapy for Enhanced Anticancer Drug Design

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ABSTRACT
Cancer is a deadlier disease now a day. Heterocyclic compounds are playing a crucial role for the treatment of cancer. Numerous anti-cancer agents are available in market which contain heterocyclic ring. Among the heterocyclic ring thiadizole is of great interest in the recent era due to their potential anti-cancer activity. Histone deacetylases (HDAC) is a crucial player in oncogenesis, proliferation, differentiation, DNA repair, up-regulation of silenced tumor suppressors, and tumor progression. Therefore, it is become a promising target for cancer drug design. This review explores the chemical structure of thiadiazole derivatives, anticancer activity and binding analysis of HDAC inhibitors from the year 2019 to 2024. Through comprehensive examination of thiadiazole scaffold containing derivatives. Overall, this review underscores the pivotal role of HDAC inhibition and guiding the rational design of next-generation anticancer agents targeting this pathway.
Keywords: Anti-cancer, Thiadiazole, HDAC, Mechanism, Structure activity relationships.

Introduction
Cancer is a second leading cause of death world-wide after the cardiovascular diseases [1]. The risk of cancer increasing day to day due to poor diet, less physical activity, junk food, some medicine, smoking, alcoholism etc. According to National Cancer Institute (NCI) in United States about 2,001,140 new cases of cancer will be detected in 2024 and 611,720 people will die from cancer [2]. The literature review of statistical and clinical data revealed that the currently available anticancer medicine have less safety and cause drug resistance due to non-selectivity of target. Therefore, there are urgent needs for the development of newer anticancer agent with target specificity and less resistance property [3]. Heterocyclic compounds play an important role for the development of potent anticancer agents. Among them thiadiazole is one of the promising nucleus and favored for anticancer activity in the current era. Structurally, thiadiazole is a five-member heterocyclic ring that contains one sulfur and two nitrogen heteroatom. Thiadiazole ring containing compounds showed diverse range of therapeutics activity such as antidiabetic [4], antioxidant [5], anticancer [6], anti-inflammatory [7], insecticidal [8] , Antiviral [9], antibacterial [10], anticonvulsant [11]. Anticancer agents exert their effect by cell suppression and inhibition of several enzymes, growth factor such as histone deacetylase (HDAC), thymidylate synthase (TS), telomerase enzyme, topoisomerase enzyme, methionine aminopeptidase (MetAP), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), focal adhesion kinase (FAK) and glycogen synthase kinase-3 (GSK-3), etc [12]. Thiadiazole scaffold has gaining attention due to its potential anticancer activity against different types of cancers by suppressing the enzymes and growth factor which are responsible for cancer. Among the entire target, HDAC is gaining more attention. HDAC mainly regulates cell proliferation, differentiation, gene expressions and

transcription. Literature review revealed that thiadiazole scaffold containing derivatives showed potent anticancer activity by inhibiting the activity of HDAC [13]. HDACs play an important role in regulating histone acetylation and modulating various signaling pathways that involve in cancer development. Histone is a protein present in a cell nucleus that is responsible for converting DNA into nucleosomes. Histones undergo dynamic modifications through the action of two enzymes [14]. The enzymes responsible for adding acetyl group to histones are HAT, while those responsible for removing the acetyl group are known as HDACs [15]. The expression of HDAC is linked with the onset and progression of tumors. The histone acetylation plays an important role in regulation of gene expression [16, 17]. The disruption of the balance between HDACs and HATs elevated the level of histone deacetylation. Elevated levels of HDACs contribute to a significant decrease in histone acetylation. This leads to a more compact chromatin structure that is unfavorable for transcriptional activation (**Figure 1**) [18]. As a result, the typical expression of specific genes at their respective DNA-binding sites is suppressed. When elevated levels of HDAC lead to the transcriptional repression of specific genes, particularly those that function as tumor suppressors or are involved in other antitumor mechanisms, it can be empirically deduced that high HDAC expression indirectly contributes to both the initiation and progression of tumors.

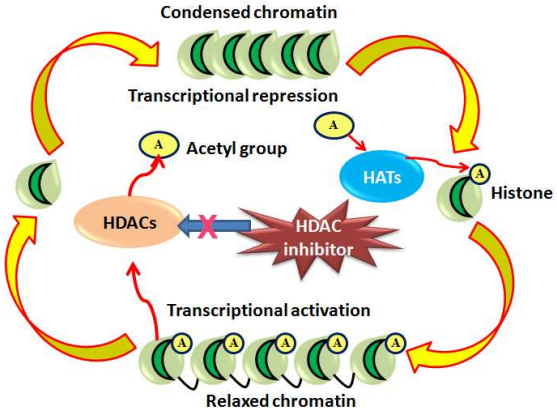


Figure 1: HDAC is affect chromatin remodeling and restore the balance between HAT and HDAC

Presently, the United States Food and Drug Administration (FDA) and the National Medical Products Administration (NMPA) of China have granted approval to several HDACi [19, 20]. While these drugs have shown promising results in treating hematological malignancies, their efficacy as standalone treatments for solid tumors often falls short. For example, we have observed limitations in the effectiveness of HDACis in one such case involving urothelial carcinomas [21]. Therefore, there is an urgent need to formulate HDACi-based combination therapy strategies or to design more selective HDACi to improve the efficacy of HDACi in solid tumors. This review highlights a comprehensive overview of thidiazole scaffolds including structure, classification of HDAC, mechanism of action and therapeutic potential of various thiadiazole derivatives on different HDAC enzymes and act as anticancer potential.

chemistry of thiadiazole

Thiadiazole moiety is a five membered heterocyclic compound belonging to the azole category. The ring is composed of one sulfur and two nitrogen atom, nitrogen atoms are interconnected with electron deficient two carbon atoms along with a lone pair of electrons of sulphur. Thidiaozle ring follow huckle rule and it behave as an aromatic compound. Thidiazole have high thermotic stability and an electron deficiency. Thiadiazole carrying mercapto, hydroxyl, and amino substituents can exist in many tautomeric forms. Thiadiazole ring is a bioisostere of pyrimidine, oxadiazole, oxazole and benzene. Based on the position of sulfur and nitrogen in thidiazole ring, four constitutional isomers are formed. All isomers: 1,3,4- thiadiazole, 1,2,4-

thiadiazole, 1,2,5- thiadiazole and 1,2,3-thiadiazole are shown in **Figure 2**.

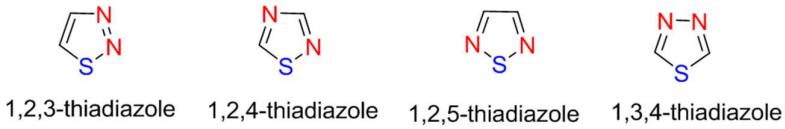


Figure 2: Different isomers of thiadiazole scaffold

histone deacetylase (HDACs) enzyme

In cancer HDACs are over expressed and lead to de-acetylation of lysine residues of both histone and non-histone substrate. HDAC play an important role in regulating several cellular processes, like cell cycle, apoptosis, and cell proliferation. HDAC influence the transcription of many genes, including cell cycle kinase inhibitor p21 (WAF1), to control cell cycle progression and proliferation [22, 23]. Importantly, elevated expression of HDAC proteins is associated with poor prognosis in patients with a variety of cancers, including gastric, ovarian, and prostate and multiple myeloma [24-26]. In humans, there are 18 HDAC enzymes that use either zinc- or NAD^+-dependent mechanisms to deacetylase acetyl lysine substrates. Although removal of histone acetyl epigenetic modification by HDACs regulates chromatin structure and transcription, deacetylation of non-histones controls diverse cellular processes. HDAC inhibitors are already known potential anticancer agents and show promise for the treatment of many diseases. Four HDAC inhibitors have been approved by the Food and Drug Administration (FDA) for treatment of cancer Vorinostat (Zolinza®) (SAHA) [27, 28], belinostat (Beleodaq®), romidepsin (Istodax®), and panobinostat (Farydak®) shown in **Figure 3** [29-31].

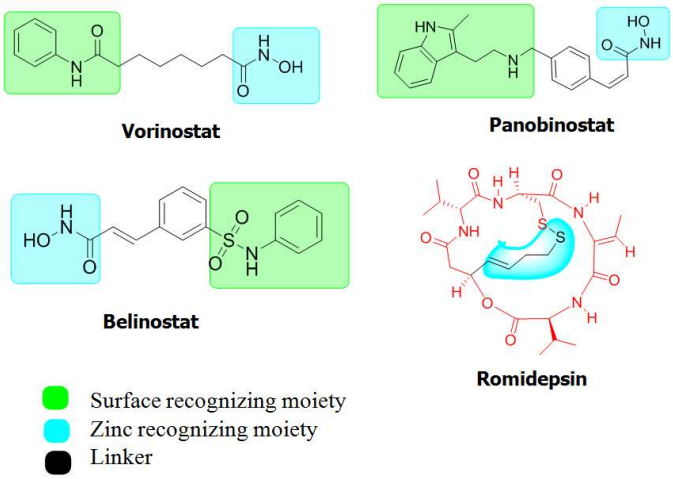


Figure 3: Structural features of the approved HDAC inhibitors with highlighted pharmacophore

Thiadiazole as HDAC inhibitor

Rusul Mohammed Hasan Ali et al., 2024, have designed and synthesized derivatives of 1,2,4-thiadiazole with zinc-binding group. All three derivatives were subjected for anti-proliferative activity assay against colon cancer cell line with taking SAHA as a standard drug. Compound **1** and **2** showed more potent anti-proliferative activity against colon cancer cell line with IC_{50}= 1.00 µM and 1.44 µM respectively compared to SAHA standard drug (IC_{50}= 3 µM). Synthesized compound **1, 2** and **SAHA** (standard analog) was docked with The HDAC2 (PDB: 4LXZ), HDAC8 (PDB: 1T69) and HDAC6 (PDB: 5EDU). Docking score of compounds **1, 2** and **SAHA** are shown in **Table 1**. Compound **1** it showed binding with active site amino acid residues such as HIS143, GLY151, PHE152 and HIS180 of HDAC8 receptor [32].

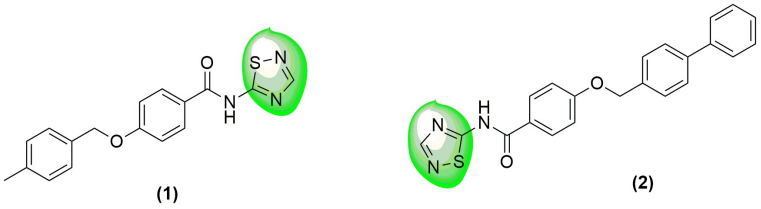
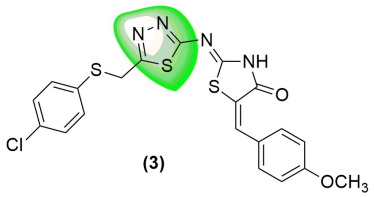


Table 1: Docking of compound 1, 2 and SAHA on HDAC receptor with PDB: 1T69

Compound No.	Docking score (kcal/mol)		
	HDAC2	HDAC6	HDAC8
mpound 1	-8.434	-7.169	-9.233
mpound 2	-8.784	-5.133	-8.677
HA	-5.613	-5.107	-4.642

Avik Maji et al., 2024 have synthesized a novel series of 21 derivatives of 1,3,4-thiadiazole. MTT assay was used to identify the cytotoxicity of all the synthesized derivatives. All the derivatives showed potent activity against breast cancer (MCF-7), MDA-MB-231 and 4T1, prostate cancer (PC3), and mouse oral squamous cell carcinoma (MOC2) cancer cell lines and normal human embryonic cell lines (HEK-293) *in comparison with* **BG45** reference anticancer molecule against the HDAC3 enzyme All the synthesized derivatives showed better selectivity on cancer cells than on normal cells. Compound **3** showed potent cytotoxicity against MCF-7 cell lines with IC_{50} value of 3.85 µM and promotes apoptosis. Also, compound **3** induces intracellular ROS accumulation and subsequent nuclear fragmentation [33].



Noor M. Mohammed *et al.,* 2023 have synthesized a series of thiadiazole derivatives and evaluated in-vitro cytotoxicity and HDAC inhibitory activity. Compounds **4** and **5** reported as potent cytotoxic agents. Compound **4** showed potent cytoxicity against both breast cancer cell line (MCF-7) and human colon adenocarcinoma (HRT-18) with reference to SAHA standard drug, while Compound **5** showed activity against only breast cancer cell line (**Table 2)**. Molecular docking study revealed that C=S moiety showed good binding affinity to the zinc binding group of the HDAC receptor (PDB: 4QA0) [34].

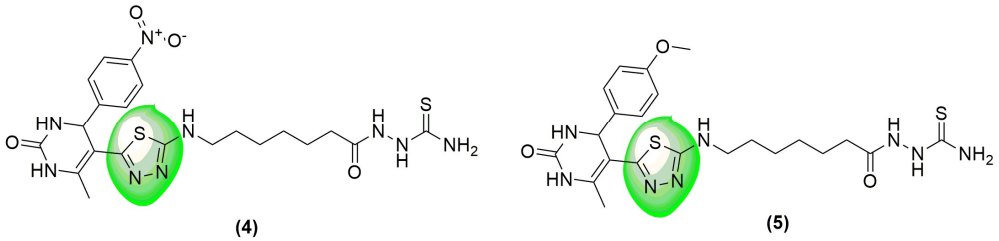
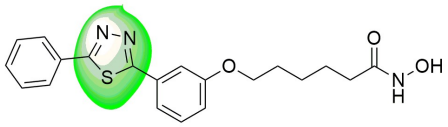


Table 2: Molecular docking and cytotoxicity of thiadiazole derivatives

Compound Name	Docking Score (kcal/mol)	Binding residues	CF-7 IC_{50} (µM)	HRT18 IC_{50} (µM)
4	-8.17	Gly151, Asp101, His142, His143	0.65 µM	65.61 µM
5	-8.21	Gly151, Tyr306, His143	0.71 µM	-
SAHA	-8.69	Tyr306		

Chen Chen et al., 2022 have designed and synthesized a series of 1,3,4-thiadiazole hydroxamate derivatives as HDACi. Among synthesized derivatives, **6** showed highest HDAC1 inhibitory activity with IC_{50} of 15 nM and potent anti-proliferative activity against MC38 cell lines with reference to SAHA standard drug. Compound **6** enhanced the acetylation of histone H3 and α-tubulin, as well as promote the activation of caspase 3 in both HCT116 and MC38 cell lines [35].



(6)

Future perspectives and conclusion

Cancer is dreadful condition which is responsible for the leading causes of death all over the world. Due to which there is need to develop novel and effective therapeutic agents which treat cancer more effectively without damaging or harming healthy cells of body. Targeting HDAC enzyme in cancer is an attractive strategy for development of highly potent anticancer molecules. Currently available HDAC inhibitors are affect the numerous subtype of HDAC and causes severe adverse effects, interfere with other body functions and causes toxicity. Cancer specific HDAC isomer inhibitors should be developed to reduced toxicity and enhances therapeutic activity of molecules. Due to hematological abnormalities and gastrointestinal problems, HDAC inhibitors are not recommended for long period of time. To omit these adverse effects, target specific HDAC inhibitor can be developing using various in-silico drug design techniques. To improve the efficacy and potency of HDAC inhibitors against cancer efforts have been made to use HDAC inhibitors along with other therapeutic agent. A comprehensive study on anti-cancer activity of thiadiazole derivatives, structural diversity of thidiazole derivative as HDAC inhibitors for the treatment of cancer is the highlight of this review. We also reported the structural features of FDA approved HDAC inhibitors such as Vorinostat, belinostat, romidepsin, and panobinostat. Based on the extensive literature examination, this review concludes that thiadiazole derivatives show potential chemo preventive and chemotherapeutic activity for the treatment of cancer. Till date, HDAC is potentially one of the safest identified cancer targets, it differentiates the normal and cancer cells based on the differences in isomer of HDAC. HDAC targeting has recently caught attention of researchers as one of the potential approaches for cancer treatment.

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Conflict of interest

The authors declare no conflict of interest.

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