**EAS Journal of Pharmacy and Pharmacology**
*Abbreviated Key Title: EAS J Pharm Pharmacol*
ISSN: 2663-0990 (Print) & ISSN: 2663-6719 (Online)
Published By East African Scholars Publisher, Kenya

Volume-8 | Issue-6 | Nov-Dec- 2026 | DOI: https://doi.org/10.36349/easjpp.2026.v08i06.004

OPEN ACCESS

**Review Article**

# Design and Synthesis of Novel Compounds Targeting Epigenetic Enzymes: Histone Deacetylases and Methyltransferases

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**Article History**
**Received:** 13.09.2026
**Accepted:** 06.11.2026
**Published**: 16.11.2026

**Journal homepage:**
https://www.easpublisher.com

**Quick Response Code**

**Abstract:** Histone modifications, primarily involving histone acetylation and methylation, have been identified as another key hallmark of cancers, inflammatory diseases, and neurodegenerative disorders. In consequence, the development of histone deacetylase inhibitors (HDACi) and histone methyltransferase (HMT) inhibitors, including lysine-specific methyltransferases, such as EZH2 and DOT1L, and arginine methyltransferases, like PRMT5, have become a druggable target of substantial pharmaceutical interest. This review compiles the structural approaches, chemical synthesis methods, and SAR profiles of small molecules targeting HDAC and HMTs from 2019 until 2025. In addition, an understanding of the classical zinc-binding group/linker/cap pharmacophore of the HDACi is described together with new warheads designed to circumvent DNA damage. The design approaches considered for HMTs are cofactor-competitive (SAM-competitive), substrate-competitive, and allosteric/MTA cooperative, with focus on the development of chemotypes for EZH2, DOT1L, and PRMT5 that are heading towards clinical development. The various synthetic pathways for each compound family (solid-phase peptide synthesis, amide formation, click chemistry, and structure-guided fragment optimization) have been reviewed along with their potencies and selectivities as described in the literature. In addition, approaches to targeting multiple targets, combinatorial therapy for epigenetics, computational design, and the translational barriers facing epigenetics are critically reviewed. It is clear that the most promising approach is mechanism-based selective inhibition.

**Keywords:** Histone Deacetylase, Histone Methyltransferase, Epigenetic Inhibitors, Drug Design, Medicinal Chemistry, EZH2, PRMT5, Structure-Activity Relationship.

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## 1. INTRODUCTION

The process of epigenetic regulation-involving heritable changes in gene expression not due to changes in the DNA sequence-itself depends on the orchestrated function of chromatin-modifying enzymes that have been categorized into 'writers', 'erasers' and 'readers'. In this regard, reversible acetylation of histone lysines catalyzed by HATs and HDACs in opposite directions and the reversible methylation of histone lysine/arginine catalyzed by HMTs have been amongst the most well-studied and pharmaceutically targetable mechanisms in the regulation of chromatin architecture [3]. Disturbance in the normal function of these enzymes through overexpression, gain-of-function mutations and mislocalization causes remodeling of chromatin structure leading to either silencing of tumor suppressor genes or activation of oncogenes and has been involved in hematological cancers, solid tumors, fibrotic disease, neurodegeneration and metabolic disease [1-19].

"Cancer continues to dominate epigenetics drug discovery, as evidenced by its continuously increasing burden worldwide [1]." Six inhibitors targeting histone deacetylases (vorinostat, romidepsin, belinostat, panobinostat, chidamide/tucidinostat and, most recently, givinostat) have been approved as drug candidates, indicating the potential of HDACs as druggable anticancer targets [4-20], while some HMT inhibitors, such as the EZH2 inhibitor tazemetostat and the PRMT5 inhibitors GSK3326595 (pinometostat/onvansertib-type series) and JNJ-64619178 have moved into the clinic [23-32]. Even with these achievements, the first generation of drugs suffers from the shortcomings of having narrow therapeutic index, non-specific

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metalloenzyme inhibition, low isoform selectivity, and metabolic instability, motivating continued design of structurally novel, mechanistically refined compounds [11-16].

This paper offers a comprehensive discussion of the rational design and synthesis of new HDAC and HMT inhibitors, based on findings from the medicinal chemistry literature that appeared mainly from 2019 to 2025. The biological basis for designing drugs against these two families of enzymes is described in Section 2. In Sections 3 and 4, the classes of HDAC and HMT inhibitors, their pharmacophores, design concepts, some representative syntheses and SARs are presented. Dual/multi-target epigenetics-based approaches are considered in Section 5, while Section 6 highlights the computational resources for inhibitor design. Challenges in translating the design of inhibitors to clinics are discussed in Section 7 critically discusses translational challenges before concluding perspectives are offered in Section 8.

## 2. Epigenetic Enzymes as Drug Targets

Acetylation of histone results in the neutralization of the positively charged ε-amino group of lysine residues, resulting in disruption of interactions between histones and DNA and causing an open chromatin conformation, while deacetylation by HDAC enzymes leads to the opposite effect on chromatin structure and transcription [20]. Histone methylation changes the chromatin transcription state depending on the protein domain interacting with methylated lysine; for instance, tri-methylation of histone H3 at lysine 27 (H3K27me3), catalyzed by EZH2, is a classical repressive mark, while methylation of H3K79 by DOT1L is usually associated with transcription activation and is misregulated in MLL-rearranged leukemias [21-25]. Since these marks are dynamic, the pharmacological targeting of enzymes that add or remove them provides an opportunity to reverse pathologically altered transcription states without genomic modifications.

## 3. Histone Deacetylases: Classification, Design, and Synthesis

### 3.1 Classification and Catalytic Architecture

Eighteen isoforms of human histone deacetylases (HDACs) can be classified into four classes on the basis of their sequence similarity to yeast homologues (Table 1). Classes I, IIa, IIb, and IV use a conserved arginase-like fold, requiring Zn2+ ion in their active sites for enzyme activity; class III sirtuins (SIRT1-7) are structurally distinct proteins that utilize NAD+ as a cofactor for their enzymatic activity [16-18]. Isoforms belonging to class I (HDAC1, 2, 3, 8) have ubiquitous expression pattern within nuclei and are strong tumor-promoting candidates; class IIa/b (HDAC4-7, 9, 10) are found both in nucleus and cytoplasm and regulate cytoskeletal and immune function, with HDAC6 deacetylating non-histone proteins like α-tubulin and HSP90 and HDAC11, the sole class IV member, has emerging roles in immune regulation [17, 18].

**Table 1: Classification of the eighteen human HDAC isoforms**

| Class | Members | Cofactor / Fold | Predominant Localisation |
|---|---|---|---|
| I | HDAC1, 2, 3, 8 | Zn2+ / Arginase fold | Nuclear |
| IIa | HDAC4, 5, 7, 9 | Zn2+ / Arginase fold | Nucleo-cytoplasmic shuttling |
| IIb | HDAC6, 10 | Zn2+ / Arginase fold | Predominantly cytoplasmic |
| III (Sirtuins) | SIRT1–7 | NAD+ / Rossmann fold | Nuclear, cytoplasmic, mitochondrial |
| IV | HDAC11 | Zn2+ / Arginase fold | Nuclear |

### 3.2 The Classical HDAC Inhibitor Pharmacophore

Almost all HDACIs that depend on zinc as an essential component are described according to a pharmacophoric hypothesis, which consists of three components: (i) the zinc binding group (ZBG), (ii) the linker region, which resides in the hydrophobic channel, and (iii) the recognition group, which binds to amino acids located in the active-site pocket [16-19]. Hydroxamic acid continues to be the most utilized ZBG due to its affinity and capacity to chelate zinc in a bidentate manner, and it can be found in all currently FDA-approved pan-HDACIs (vorinostat, panobinostat, belinostat, givinostat); however, hydroxamates are susceptible to metabolism through glucuronidation and hydrolysis processes, leading to safety concerns related to off-target inhibition of metalloenzymes and genotoxicity in non-oncology conditions [16-20].

This has resulted in systematic investigations of different alternatives of ZBGs-ortho aminoanilides/benzamides (entinostat, chidamide, mocetinostat) that provide class I selectivity by a slow entropy-favored mode of binding; cyclic depsipeptide thiols (romidepsin); mercaptoacetamides; trifluoromethyl ketones; and oxadiazoles-each providing selective and pharmacological properties [16-18]. In addition to this, a novel design approach where the metal chelation group is completely absent has been discovered; these HDACIs do not possess the zinc-binding property but exhibit the same efficacy and isoform selectivity as compared to hydroxamic acid HDACIs without having any electrophilic mutagenic properties [1].

### 3.3 Structure-Based Design Strategies

Modern HDACi optimization strategies usually begin by scaffold hopping starting from a known cap/linker/ZBG scaffold based on co-crystal structures of HDAC1, 2, 6, 7, or 8 bound with their reference inhibitors. The cap group diversity is the main approach

towards isoform selectivity, since bulky and inflexible aromatic caps (such as indazole, quinazolinone, coumarin, phenylisoxazole scaffolds), which do not fit into the narrow pocket of the class I channel, selectively target HDAC6, while small and planar benzamide caps are class I selective by virtue of using the foot pocket that exists only in HDAC1-3 [6-10]. In turn, Podili *et al*., designed HDACi from 4-(2-aminoethyl) phenol by using virtual screening and molecular docking followed by synthesis and enzyme tests, providing a workflow which is now standard practice [2]. In a similar manner, Nasrollahzadeh *et al*., developed imidazole-fused benzamides and hydroxamates that featured enhanced activity and selectivity compared to the anilide series previously used as leads due to the presence of the imidazole group [7], while the coumarin-containing hydroxamates of Yang *et al*., displayed subnanomolar inhibitory activity against HDAC1, almost ninety times stronger than vorinostat through optimisation of linker length and cap rigidity [9].

Design of HDAC6-selective molecules has gained considerable interest because of the involvement of the enzyme in neurodegeneration, autoimmunity, and tumor immune escape, as well as its shallow catalytic tunnel, which allows bulky caps. Quinazolin-4-one derivatives of HDAC6 inhibitors developed by Wan *et al*., used this property for achieving selective and potent (<1μM) inhibition with good cellular activity [6], and selective HDAC6 inhibitors have been widely described in terms of their immunomodulatory properties [8]. Similarly, selective HDAC8 inhibitors have been developed for treatment of acute myeloid and lymphoblastic leukaemias by taking advantage of subtle structural differences in the HDAC8 foot pocket as compared to other class I enzymes [12]. In addition to cap modifications, kinetic selectivity - slow, tight-binding inhibition that uses isoform-specific conformational dynamics-has been recognized as an underexploited design principle [11].

### 3.4 Representative Synthetic Strategies

The synthesis of hydroxamate type of HDACi is usually convergent in nature: preparation of cap-linker fragment by Suzuki coupling reaction, Buchwald-Hartwig cross-coupling reaction or amide coupling, followed by coupling of terminal carboxylic acid and O-protected hydroxylamine (either O-tetrahydropyranylhydroxylamine or O-benzylhydroxylamine), which is ultimately followed by deprotection under acidic/hydrogenolytic conditions [2-9]. The synthesis of benzamide type of HDACi is generally achieved by amide coupling of a cap fragment having an aniline group and a carboxylic acid bearing linker through usual amide couplings (HATU/EDC and HOBt). For cyclic peptide-type HDACi such as depsipeptide analogs, solid phase peptide synthesis and macrolactamization of 6-tetrapeptide macrocycles are used, with strict control on diastereoselectivity during the formation of macrocycle rings. Of late, SuFEx reaction has been employed in the solid phase compound library synthesis for the development of novel HDACis, which involves the simultaneous synthesis and screening of ZBG/linker/cap combinations [13]. Click chemistry (copper-catalysed azide-alkyne cycloaddition) has likewise been used to construct focused HDAC1/2-selective libraries from a triazole-linked scaffold, permitting efficient exploration of linker geometry [5].

### 3.5 Structure-Activity Relationships

The following common SAR observations can be made from the literature. First, the linker chain of five-six methylene equivalents is optimal for positioning the hydroxamate group for zinc chelation in Class I/II enzymes; deviation results in decreased activity by one-two orders of magnitude [9-17]. Second, planar aromatic cap groups containing hydrogen bond acceptor increase interaction with the surface rim and, when coupled with the ortho-aminoanilide ZBG, result in a pronounced class I vs. Class IIb selectivity [7-14]. Third, incorporating heteroatoms (imidazole, isoxazole, indazole) into the cap increases aqueous solubility and metabolic stability compared to carbocyclic caps [6-10]. Fourthly, belinostat derivatives having modifications to their sulfonamide linkers maintain nanomolar potency while having enhanced selectivity compared to the parent compound, thus proving that clinically approved scaffolds still have plenty of room for optimization [14]. Lastly, substituting the hydroxamic acid-based zinc binding group (ZBG) in favor of other non-binding or hydroxamate groups can help retain potency but minimize electrophilic/mutagenic risks, which is increasingly relevant in non-oncological chronic diseases like diabetes and neurodegeneration [1-19].

## 4. Histone Methyltransferases: Classification, Design, and Synthesis

### 4.1 Classification and Catalytic Mechanism

Histone methyltransferases use SAM as the donor substrate to transfer methyl group to lysines or arginines on the histone (and many other non-histone) protein substrates resulting in production of S-adenosyl-L-homocysteine (SAH) as a by-product (Table 2). There are lysine-specific methyltransferases (KMTs) that are represented by SET-containing enzymes including EZH2 – a catalytic component of Polycomb Repressive Complex 2 (PRC2) involved in H3K27 trimethylation and DOT1L – an exclusively H3K79 methyltransferase [21-25]. There are protein arginine methyltransferases (PRMTs) including types I (asymmetric dimethylation; PRMT1, PRMT3, CARM1) and II (symmetric dimethylation; PRMT5), with PRMT5 being of significant pharmacological interest because of its broad functionality in RNA splicing and DNA repair and its selective vulnerability in MTAP-deficient cancers [26-30].

**Table 2: Representative histone methyltransferase families and their disease associations**

| Family | Representative Enzymes | Methyl Donor | Disease Association |
|---|---|---|---|
| Lysine methyltransferases (KMTs) | EZH2 (PRC2), DOT1L, G9a/EHMT2, SETD2, NSD2 | S-adenosyl-L-methionine (SAM) | Lymphoma, leukaemia, solid tumours, neurodevelopmental disorders |
| Arginine methyltransferases (PRMTs) | PRMT1, PRMT3, PRMT5, CARM1/PRMT4 | S-adenosyl-L-methionine (SAM) | Mantle-cell lymphoma, MTAP-deleted cancers, splicing dysregulation |

### 4.2 Pharmacophore and Inhibition Mechanisms

Three primary strategies for inhibition have been employed in the development of HMT drugs. SAM-competitive inhibitors bind the cofactor pocket and comprise a core resembling adenine or purine (such as sinefungin derivatives used at an early stage), connected to various groups that utilize other selectivity pockets; however, owing to the high conservation of SAM binding pocket within the human methyltransferase superfamily, gaining target specificity is difficult with this strategy [27-30]. Instead, substrate competitive inhibitors bind the histone peptide binding pocket and generally exhibit higher target specificity than SAM-competitive inhibitors, as in the case of EPZ-6438/tazemetostat class EZH2 inhibitors that bind the H3K27 substrate binding pocket [23, 24]. Finally, a more recent strategy makes use of allosteric or cooperative pockets, which are only accessible with a certain cofactor bound, such as the case of MTA-cooperative PRMT5 inhibitors that selectively bind the PRMT5-MTA complex present in MTAP-deficient tumors [29-30].

### 4.3 Design Strategies for EZH2 and DOT1L Inhibitors

High-throughput screening combined with structure-guided lead optimisation efforts led to the discovery of first-generation EZH2 inhibitors, including GSK126 and GSK343, which are highly active and SAM-competitive cell-permeable pyridones [12]. The development of second-generation inhibitors has involved the pursuit of inhibitors with increased residence time at the target-a pharmacodynamic parameter whose importance for pathway inhibition is gaining increasing recognition-through the incorporation of a 4-thiomethyl pyridone moiety that increases potency and residence time over that of the first-generation inhibitors and maintains physicochemical properties [13]. Structure-based analyses of EZH2 inhibitors have classified inhibitors based on whether they occupy the SAM pocket alone, the substrate channel alone, or both, allowing for the rational choice of scaffolds for new inhibitors [23]. Since DOT1L, lacking a classical SET domain, requires novel SAM-mimicking adenosine-based inhibitors, inhibitors designed based on structure and mechanisms have proven to be highly potent and selective against lysine and arginine methyltransferases, validating DOT1L as a druggable target for MLL-rearranged leukemia [21].

### 4.4 Design Strategies for PRMT5 Inhibitors

PRMT5 inhibitors have been evolved through three generations. The earlier SAM- and substrate-competitive nucleoside-based inhibitors (bicyclic nucleosides) provided strong inhibition; however, these were limited by their narrow therapeutic index because of on-target toxicology in normal proliferating tissues since PRMT5 enzyme plays important roles in both healthy and cancer cells [26]. Further structure-aided design led to potent and selective non-nucleoside PRMT5 inhibitors having better pharmacological properties and less off-target binding affinity to other methyltransferases [27]; moreover, PPI inhibitors acting on the interface between PRMT5 and MEP50 have been explored as a different way of inhibiting PRMT5 enzyme apart from catalytic pocket [28]. A new series of PRMT5 inhibitors based on a tetrahydroisoquinoline scaffold and derived from GSK3326595 provided nanomolar activity even lower than that of its parental compound through SAR studies exploration of the core scaffold and peripheral substituents [31]. Another group of covalent PRMT5 inhibitors targeting cysteine residue (Cys449), which is present only in the PRMT5 active site, has also been developed, leading to irreversible adduction by forming hemiaminal-derived electrophiles [32]. The latest breakthrough is the development of MTA-cooperative inhibitors, which switch from the previous SAM-cooperative inhibitor class by relocating their binding mode to occupy a site in the SAM pocket that is released upon binding of the metabolic product methylthioadenosine (MTA) [29].

### 4.5 Representative Synthesis and SAR

Inhibitors of SAM-mimetic type and nucleoside-derived HMTs are usually prepared from protected adenosine or 7-deaza-adenosine scaffold through a combination of glycosylation, followed by Mitsunobu/Appel-type functionalization of the ribose hydroxyl groups, and late stage coupling for installation of the substituent that provides selectivity, and finally, global deprotection [27-29]. Non-nucleoside EZH2/PRMT5 inhibitors are usually prepared using medicinally tractable methods of construction of the aromatic scaffold through Suzuki-Miyaura/Buchwald-Hartwig cross-coupling, with subsequent reductive amination/amide coupling for installation of the solubility/selectivity confring side chain [13, 31]. Within all these series, potency is highly dependent on the capacity of the inhibitor framework to establish bidentate hydrogen bonding with active site residues (Tyr/Asp residues in the EZH2 SAM pocket or Asp419/Met420 in

PRMT5), whereas selectivity against other methyltransferases which are evolutionarily similar is controlled mainly by the substituents which extend into nearby but less-conserved sub-pocket regions [24-31]. Substituting with fluorine or heterocycles at these selectivity-defining sites has been demonstrated to be beneficial for both potency and metabolic stability of different EZH2 and PRMT5 series [13-27].

**5. Dual-Targeting and Combination Epigenetic Strategies**

Given that chromatin-modifying enzymes often function in multi-protein complexes and demonstrate pathway redundancy, combination inhibition of two epigenetic targets or one epigenetic and one non-epigenetic target has gained importance as a mechanism for overcoming resistance and enhancing effectiveness compared to monotherapy. Using high throughput screening, a powerful combination effect between the EZH2 inhibitor GSK343 and DOT1L inhibitor SGC0946 has been noted in neuroblastoma models, with the combination treatment causing ATF4-dependent endoplasmic-reticulum stress resulting in better growth suppression in tumor xenografts as compared to the individual drugs in vivo, and without affecting normal fibroblasts [21]. At the molecular level, dual pharmacophores have been developed targeting EZH2 and BRD4 or EZH2 and HSP90 for synergistically inhibiting tumors through the disruption of both chromatin reader and chaperone-mediated signaling [22-24]. Likewise, dual pharmacophore-based HDAC/kinase and HDAC/HDAC complex (such as CoREST-targeting) inhibitors employing two different pharmacophores in a single molecule structure have demonstrated efficacy in circumventing compensatory pathways in response to single-target HDACis [4]. These observations together suggest polypharmacology, either via combination therapy or single-molecule hybridization, as an important approach in the development of next-generation epigenetic drugs.

**6. Computational and Rational Design Tools**

The discovery process for new HDAC and HMT inhibitors is not done using empirical synthesis alone; rather, virtual screening, molecular docking, and pharmacophore-based techniques are now the normal first step, which helps in the identification of the target molecules and SAR. QM/MM methods were utilized to understand the electronic and geometric requirements of zinc binding group coordination, which helps in designing new alternatives to hydroxamate-based ZBGs that are metabolically stable. [17]. The structure-based mechanism-switching approach, where the comparison of co-crystal structures of an enzyme bound to various states of cofactors or metabolites is used to discover a novel and selective binding mode for a new inhibitor, played a key role in the discovery of the MTA-cooperative PRMT5 inhibitors and serves as a broadly applicable methodology for the development of inhibitors of other epigenetic cofactor-dependent enzymes [29]. Very recently, machine learning- and large language model-assisted fragment space exploration has been successfully used for optimization of lead molecules targeting PRMT5.

**7. Translational Challenges and Future Perspectives**

Even though there have been many advances, there are still a number of obstacles preventing further clinical exploitation of HDAC and HMT inhibitors. One such problem is that there has been no complete isoform selectivity with respect to most chemical classes, and pan-HDAC inhibition leads to toxicities involving the haemoglobin system and the heart, making ongoing efforts towards HDAC6/8 inhibitors warranted for non-cancer applications [8-19]. Hydroxamate-containing ZBGs, although very potent, suffer from known mutagenic effects and metalloenzyme liabilities that make them unsuitable for chronic and non-oncological diseases such as diabetes and neurological conditions, emphasizing the importance of developing alternative, non-hydroxamate/non-chelating ZBGs [1-19]. Regarding HMT inhibitors, selectivity for the highly conserved SAM binding site is one of the biggest challenges for medicinal chemists, and on-target toxicity in proliferating cells prevented the further clinical exploitation of several early PRMT5 inhibitors [26-30]. Last but not least, acquired resistance via target mutation, pathway compensation, or up-regulation of other chromatin modifiers has been noted with both HDAC and EZH2 inhibitors in clinical studies, thus offering more evidence for the rationale of combined therapies and dual-targeting approaches mentioned in Section 5.

With regard to future perspectives, key focus areas could include: (i) extensive research into non-hydroxamate and non-chelating ZBG compounds to widen the scope of potential use of HDAC inhibitors outside of oncology; (ii) development of genotype-specific epigenetic treatment based on cooperative binding modes with cofactors and/or metabolites, in line with the example of PRMT5 inhibitor with MTA; (iii) machine learning-based scaffolding together with structure-based validation for efficient lead optimisation; and (iv) combination or hybrid molecule design to prevent resistance.

## 8. CONCLUSION

Histone deacetylases and histone methyltransferases continue to be two of the most pursued classes of epigenetic drug targets. In recent years, a clear trend in design strategy can be seen from potent pan-inhibitors to isoform-specific inhibitors using the principles of mechanism-directed designs such as cap group diversification, alternate zinc coordination motifs, substrate/cofactor cooperativity, and rational polypharmacology. Future progress through the use of structure-based design approaches, synthetic techniques such as click and SuFEx chemistry to rapidly generate

compound libraries, and computational approaches is anticipated.

**Conflicts of Interest:** The authors declare no conflicts of interest.

**Funding:** This research received no external funding.

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**Cite This Article:** Shahi, S. K., Gupta, V., Malik, J. K., & Arya, S. (2026). Design and Synthesis of Novel Compounds Targeting Epigenetic Enzymes: Histone Deacetylases and Methyltransferases. *EAS J Pharm Pharmacol, 8*(6), 120-126.
https://doi.org/10.36349/easjpp.2026.v08i06.004