De Remediis
ISSN: 3058-0358
Official Scientific Journal of Faculty of Pharmacy UD

Review

Medicines for influencing the posttranslational modifications of histones – a tutorial review

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Abstract

Epigenetic therapy is a relatively novel, but undoubtedly a promising area of pharmacology. Most epigenetic drugs act by affecting enzymes and play a role in post-translational modifications of histones. The molecular targets of these medicines include histone methyltransferases, histone demethylases, isocitrate dehydrogenases, histone acetyltransferases and histone deacetylases. Since histone modifications are important regulatory signals, abnormalities in this process often lead to tumorigenesis, therefore these medicines constitute an important class of antitumor therapy. In this tutorial review, we would like to briefly overview the medicines that affect histone modifications, focusing on the currently approved ones, and briefly mention other interesting examples.

1. Introduction

The word epigenetics (meaning above genetics, i.e. factors beyond the genetic code) can be traced back into the 1940s. The term is based on the observation that the same genetic background (base sequence of DNA) could lead to different heritable traits. It shows that the expression of genes can be modified without altering the base sequence. The main epigenetic reagulations are gene silencing via noncoding RNA, chemical modification (mostly methylation) of DNA without changing the nucleotide sequence, and chemical modifications of the histones[1-6].

Histones are proteins that are responsible for the formation of a higher order structure called nucleosome, in which a 146 base pair DNA segment is coiled around a histone octamer consisting of 2-2 H2A, H2B, H3 and H4 molecules of histone.

Histone H1 is responsible for anchoring DNA in the nucleosome. The nucleosome and histone H1 together forms, the chromatosome. Through this mechanism, histones play

a crucial role in packaging DNA into a more compact form to be able to fit into the nucleus. Histones can go through several posttranslational modifications (PTMs) such as phosphorylation, ubiquitination, ADP-ribosylation, citrullination, SUMOylation, methylation or acetylation. These modifications alter the structure of chromatin, thus affecting gene expression. The most sterically accessible part of the histones is the so-called tail of the N-terminal region, especially the relatively long tails of the H3 and H4. The most important modifications are acetylation and methylation (mono, di-, or trimethylation) of arginine and lysine residues. The biological effect depends on both the type and exact location of the modification. Acetylation of histones mostly occurs on the lysines of the H3 tail. Lysine acetylation decreases histone-DNA binding, leading to a more open chromatin structure, which offers DNA more accessible to enzymes of transcription (gene activating effect). Methylation, however, can be either activating or silencing. For example, trimethylation of the 27th lysine residue of the histone H3 (H3K27, where K is the single-letter code for lysine) decreases, while H3K4 methylation activates gene expression[1,2,4,5]. The incorporation and cleavage of these groups are strictly regulated and carried out by specific enzymes: histone acetyltransferases (HAT) are responsible for the acetylation of histones, histone deacetylases (HDAC) cleave the acetyl groups from histones, histone methyltransferases (HMT) mediate methylation of histones and histone demethylases (HDM) remove methyl groups. The enzymes performing post-translational substitutions are often referred to as writers, while while cleaving enzymes are called erasers[7]. Disruption of normal epigenetic patterns plays roles in the pathophysiology of a wide range of diseases, including neurological, cardiac and tumor diseases. For example, lysine-specific demethylase-1 (LSD-1) mutation is found in various tumors[1,2,3]. The currently approved pharmacons targeting histone-modifying enzymes are mainly used in the latter indication as anticancer agents.

In this tutorial review, we briefly summarize the medicinal chemistry, pharmacology and mechanism of action of the drugs that interfere with the posttranslational modifications of histone proteins, focusing on the currently approved ones.

2. Pharmacons

The medicines currently used in this area can be classified into the following groups: histone methyltransferase inhibitors (HMTi, metostats), histone demethylase inhibitors

(HDMi), isocitrate dehydrogenase inhibitors (IDH inhibitors, sidenibs), histone acetyltransferase inhibitors (HATi) and histone deacetylase inhibitors (HDACi).

2.1 ***Histone methyltransferase inhibitors (HMTis, metostats)***

HMT inhibitors block the methylation of histones, causing histone hypomethylation.

Tazemetostat: tazemetostat was approved in 2020 by the FDA for the treatment of patients over 16 years with metastatic or locally advanced epithelioid sarcoma not suited for surgical resection as the first specific treatment in this indication. It has also received orphan designation for the treatment of other types of cancer in the US and in the EU. It should be taken orally. Tazemetostat is a selective inhibitor of the enhancer of zeste homolog 2 (EZH2), the catalytic subunit of a multiprotein complex, the polycomb repressive complex 2 (PRC2), which catalyses the methylation of lysine 27 of histone H3. Hyperactivity causing EZH2 mutations can be detected in several cancer types, such as epitheloid sarcomas. Tazemetostat is mainly metabolized by CYP3A, therefore, its co-administration with CYP3A inhibitors is not favorable[8,9].

Valemetostat: valemetostat was approved in Japan in 2022 for the treatment of relapsed or refractory acute T-cell lymphoma (R/R ATL). Valemetostat is an ihibitor for both EZH1 and EZH2, thus blocking the methylation of H3K27 position. Valemetostat is used orally as a tosylate salt[10,11].

Both tazemetostat and valemetostat are 3-substituted 4,6-dimethyl-2-pyridone derivatives and act as competitors for the S-adenosylmethionine (SAM, the methyl donor cofactor of histone methylases including EZH) for binding to the SET domain of EZH[10]. The structural similarities between the two compounds are highlighted in **Figure 1**.

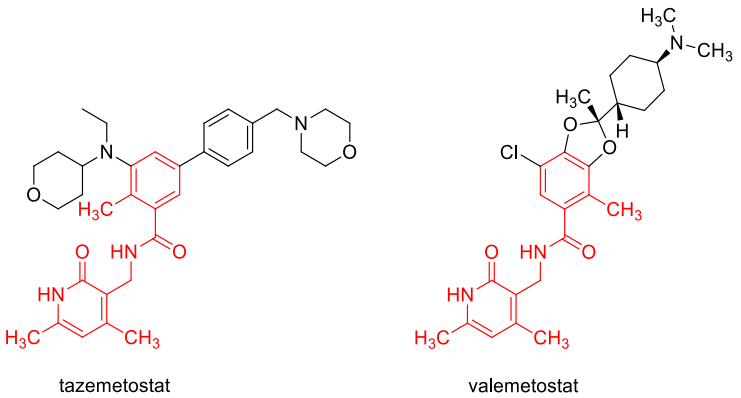


Figure 1*.:* Structures of tazemetostat and valemetostat, the analogous motifs are highlighted in red.

The most important HMTis belong to the same structural and farmacodynamic family as tazemetostat and valemetostat. Among others, it is worth mentioning pinometostat, which contains an adenosine analogue motif. Pinometostat (**Figure 2**) is an inhibitor of DOT1L histone methyltransferase, thus inhibiting the H3K79 methylation. However, it is currently not approved[1,12].

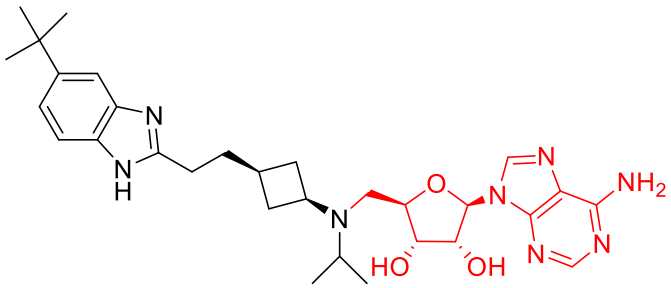
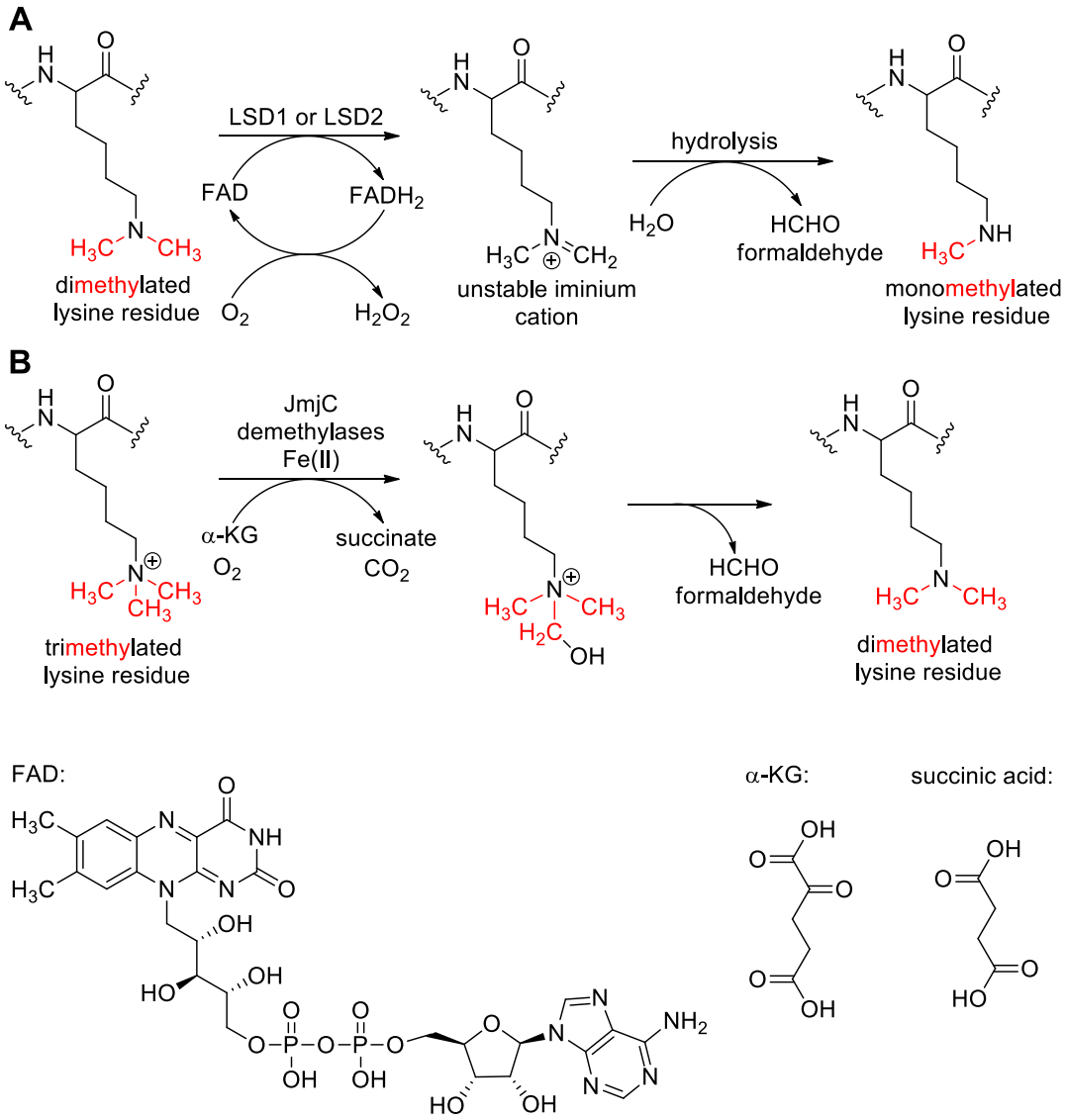


***Figure 2**.:* Structure of pinometostat, the adenosine analog part highlighted in red.

2.2 ***Histone demethylase inhibitors (HDMis)***

Lysine demethylases can be divided into two main groups. The first group includes lysine-specific demethylase 1 (LSD1 or KDM1A) and LSD2 (KDM1B). The reaction they catalyze is an oxidative N-dealkylation, therefore they need flavin-adenine dinucleotide (FAD) as a cofactor. Because of this mechanism, a lone pair of electrons on the nitrogen is needed, therefore methyl groups from mono- and dimethylated lysine residues can be removed. The second group includes Jumonji C (JmjC) type demethylases, which are able to erase trimethyl marks, too. JmjC demethylases use Fe(II) and alpha-ketoglutarate (α-KG, or 2-oxoglutarate = 2-OG) as cofactors. The catalytic mechanism of histone demethylases is depicted in **Scheme 1**[13].



***Scheme 1**.:* Catalytic mechanism of FAD-containing lysine demethylases (**A**) and Jumonji type (**B**) demethylases.

Tranylcypromine (TPA or TCP): tranylcypromine (**tran**s-phen**yl**-**cy**clo**pro**pyla**mine**) is an irreversible monoamine oxidase (MAO) inhibitor approved for the treament of depression. It also inhibits LSD1, which has a catalytic domain, like that of the MAO. TPA acts by covalently binding to FAD, rendering it unable to act as a cofactor in the reaction. Several HDMis with a structure similar to TPA exist in various stages of development (**Figure 3.**), but until now, none of them have been approved for this indication[1,14,15].

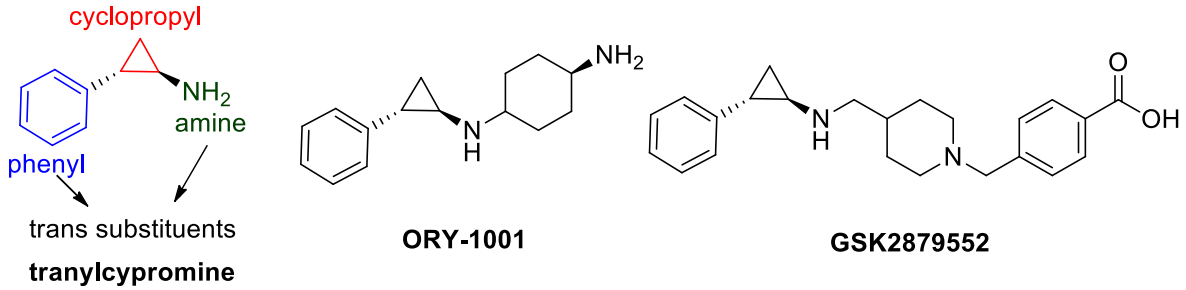


***Figure 3**.:* Structure of tranylcypromine (TPA) and TPA-based HDMis.

2.3 Isocitrate dehydrogenase inhibitors (IDH inhibitors, sidenibs)

Isocitrate dehydrogenase (IDH) enzymes play an important role in cellular energy balance by (among other functions) converting isocitrate to α-KG via oxidative decarboxylation. Gain of function mutations lead to mutant IDH enzymes, catalysing the transformation of α-KG to D-2-hydroxy glutaric acid (D-2-HG), a so-called oncometabolite. 2-HG inhibits several enzymes, using α-KG as a cofactor, including the Jumonji C domain type histone demethylases, or the ten-eleven translocation (TET) DNA demethylase enzymes. As an oncometabolite, 2-HG also plays a role in tumor progression. For example, 2-HG inhibits α-KG dependent prolyl-hydroxylase (PHD), which normally hydroxylates HIF-1α (hypoxia induced factor alpha) proline residues, rendering it inactive. In hypoxic conditions, the above reaction cannot take place, leading to HIF-1α stabilization and expression of several genes that are regulated by HIF-1, including genes involved in angiogenesis. Briefly, 2-HG promotes angiogenesis through inhibiting PHD, leading to pathological HIF-1α activation, increasing the tumor survival. α-KG dehydrogenase is also inhibited by 2-HG. As α-KG dehydrogenase converts α-KG to succinyl CoA, and the latter is part of the heme synthesis pathway, the heme synthesis is also blocked. This will disrupt the erythroblast differentiation, which leads to an erythroid/myeloid imbalance, causing the development of myeloid tumors[1,16].

Enasidenib (AG-221): Enasidenib was approved by the FDA in 2017 for the treatment of relapsed or refractory acute myeloid leucemia (R/R AML) in adults. Enaseidenib is an inhibitor for the mithocondrial IDH2 isoform, with relatively high selectivity (40-fold difference) against the mutant enzymes (R140Q, R172K & R172S), thus decreasing 2-HG concentration. A serious adverse effect of enasidenib is differentiation syndrome (DS), a possibly lethal complication with renal failure, hypotension, fever and interstitial lung infiltration[1,17,18].

Ivosidenib (AG-120): Ivosidenib was approved by FDA in 2018 for the treatment of R/R AML with susceptible IDH1 mutation. Unlike enasidenib, ivosidenib inhibits the cytosolic isoform of IDH1, which is more common than IDH2 mutations. Ivosidenib is highly selective for the mutant enzyme. Ivosidenib also can lead to DS, possibly due to a sudden increase in neutrophil differentiation after removal of the differentiation block[19].

Olutasidenib: Olutasidenib was approved by the FDA in 2022 for the treatment of adults with R/R AML with susceptible IDH1 mutation. It inhibits the IDH1 R132H, R132L, R132S, R132G &R132C mutant forms of IDH1 enzyme (R132H and R132C are the most common mutations in AML patients)[20].

Vorasidenib: Vorasidenib was approved in 2024 by the FDA for the treatment of adults and patients 12 years of age or older with grade 2 astrocytoma or oligodendroglioma with susceptible IDH mutations after surgery. Vorasidenib is a dual inhibitor of both IDH1 and IDH2 (for mutant and wild type). Vorasidenib was specifically designed to have increased blood-brain barrier (BBB) penetration, which makes it suitable for treating gliomas[21].

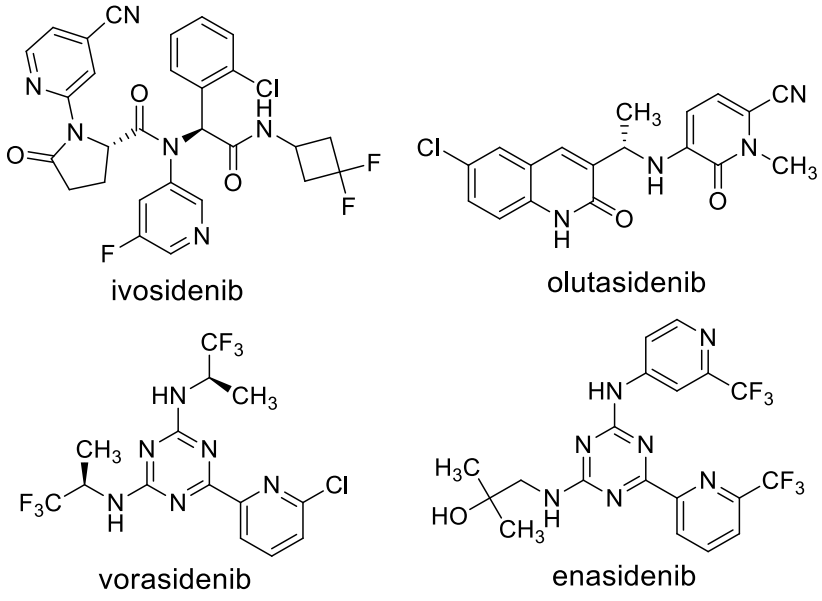


***Figure 4**.:* Structure of isocitrate dehydrogenase inhibitors.

2.4 ***Histone acetyltransferase inhibitors (HATis)***

Histone acetyltransferase inhibitors block the acetylation of histones. There are currently no approved HATi medicine, however several synthetic molecules are in different stages of development, and a few natural products such as curcumin and garcinol show HATi activity[1,22].

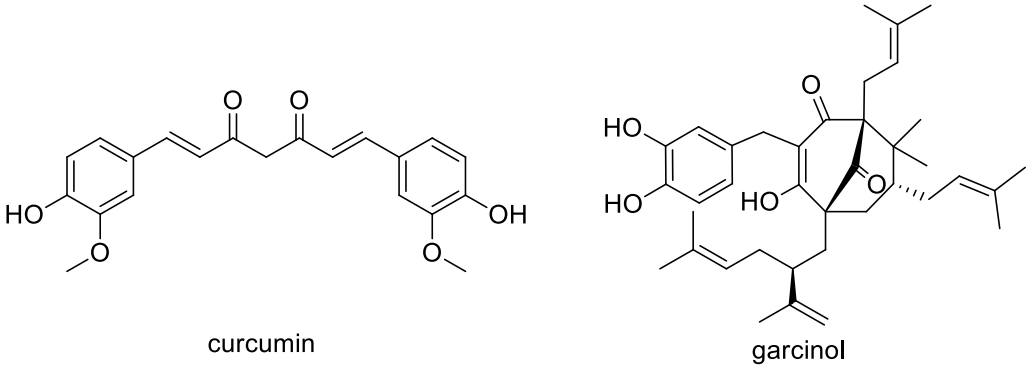


***Figure 5**.:* Structure of natural HATis.

2.5 ***Histone deacetylase inhibitors (HDACis)***

Deacetylation of histones causes chromatine condensation, hindering transcription. Histone deacetylase inhibitors can block the cell cycle in the G1 or G2/M phase, leading to apoptosis. These compounds also influence angiogenesis and tumor metastasis, making cells more sensitive to chemotherapy[1,2]. As histone deacetylases are zinc-dependent enzymes, the HDAC inhibitors contain a Zn-chelating group to block enzyme activity[23,24].

2.5.1 Hydroxamic acid derivatives

In hydroxamic acid derivatives, the Zn-chelating group is the hydroxamic acid group. Beside the zinc-bindig group (ZBG) they contain an aromatic „cap", a connecting unit (CU), which is mostly an amido, or amino group and a lipophilic linker between the ZBG and the cap-CU. The role of the cap is to bind the molecule to the enzyme, affecting selectivity. The general problem of this drug class is the poor pharmacokinetics and the relatively poor selectivity as they oftenly target other Zn-dependent proteins[25,26].

Vorinostat (suberoylanilide hydroxamic acid = SAHA): The first compound in this group of drugs. It was approved in 2006 by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL). It inhibits class I, II and IV HDAC enzymes[27].

Belinostat: Belinostat was approved in 2014 by the FDA for relapsed or refractory peripheral T-cell lymphoma (R/R PTCL). The spectrum of belinostat is similar to that of vorinostat[28].

Panobinostat: Panobinostat was approved in 2015 by FDA and EMA (in combination with the proteosome inhibitor bortezomib and the glucocorticoid dexamethasone) for

the treatment of adult patients with relapsed and/or refractory multiple myeloma. Unlike vorinostat and belinostat, panobinostat is a pan HDAC inhibitor[29,30].

Among the non-approved compounds, **trichostatin A (TSA), ricolinostat, pracinostat** and **dacinostat** deserve attention[1].

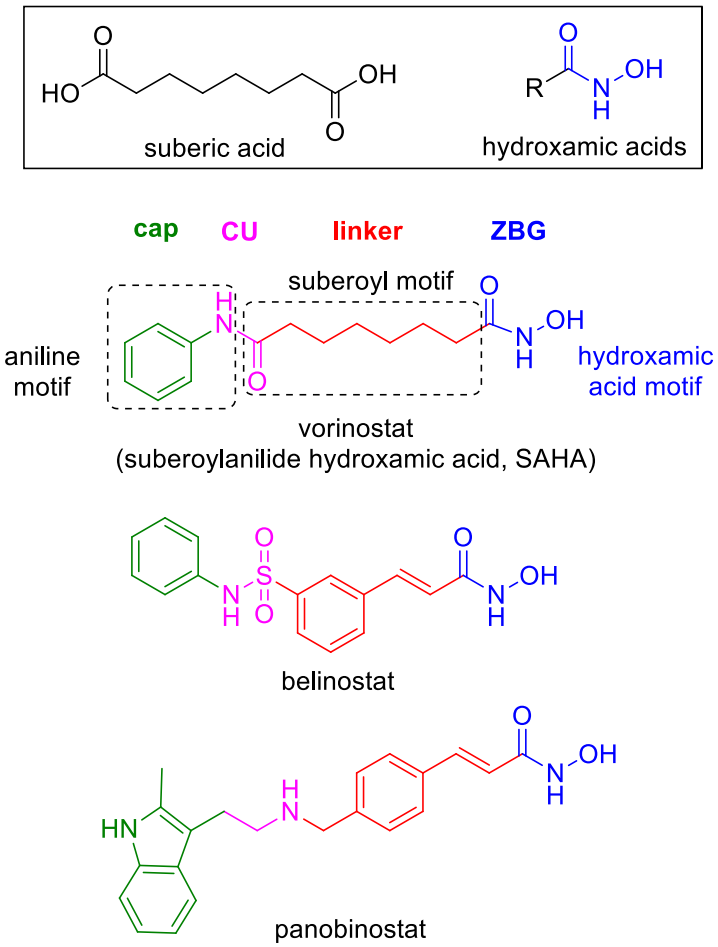


***Figure 6**.:* Structure and building blocks of hydroxamic acid-type HDAC inhibitors.

2.5.2 Benzamides

Benzamide type HDACis are similar to the hydroxamic acid derivatives, except that instead of the hydroxamic acid moiety, the ZBG is a benzamide unit. Benzamides have higher class I HDAC selectivity than that of hydroxamic acid derivatives.

Tucidinostat (chidamide): Approved in China for the treatment of R/R PTCL. Tucidinostat is an inhibitor of class I and IIb HDAC enzymes[31].

Other benzamides such as **entinostat** or **mocetinostat** are not currently approved[1,2].

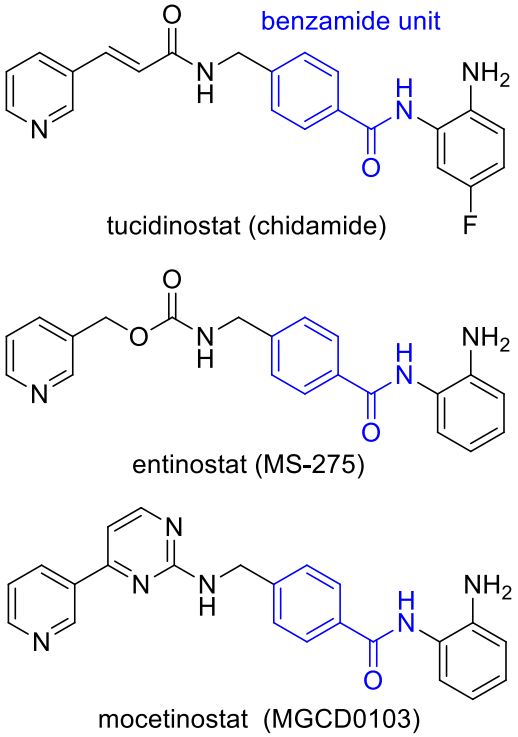


***Figure 7**.:* Structure of benzamide derivatives.

2.5.3 Cyclopeptides

Romidepsin: It was approved by the FDA for the treatment of cutaneus T-cell lymphoma (CTCL). The spectrum of romidepsin is narrower than that of the hydroxamic acids, as it inhibits class I and II HDACs. Romidepsin is a bridged bicyclodepsipeptide, which means that one of the peptide bonds is replaced by an ester bond. Romidepsin contains a disulfide bond that is reduced to 2 thiol groups by glutathione (GSH). These thiol groups are the zinc binding groups[1,32].

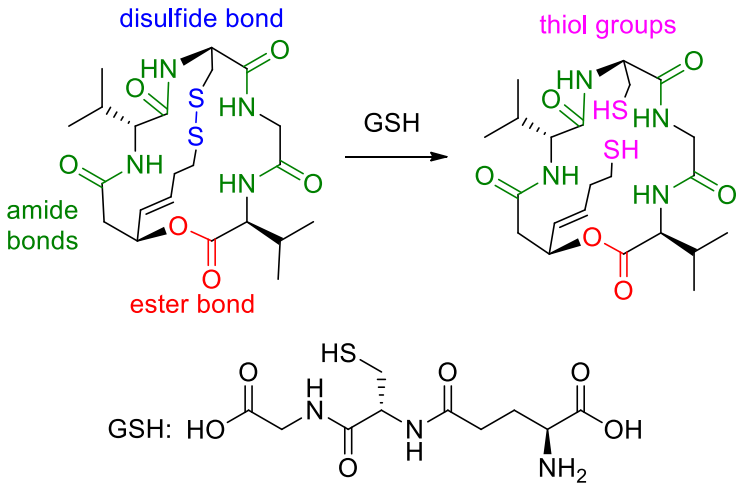


***Figure 8**.:* Structure and mechanism of action of romidepsin.

2.5.4 Carboxylic acids

The carboxyl group also can act as a weak zinc binding group, therefore carboxylic acids such as **butyric acid, phenylbutyric acid** or the antiepileptic **valproic acid** also show some HDAC inhibitor activity. They are currently not approved in this indication[1,25].

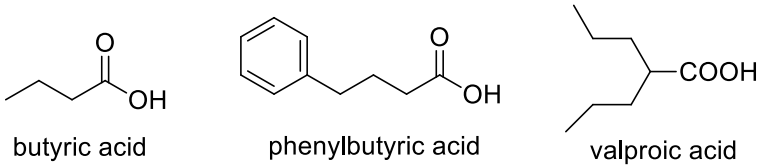


***Figure 9**.:* Structure of carboxylic acids with HDAC inhibitory activity

3. Discussion

Epigenetic therapy is a relatively new, but successfully and dynamically developing field in medicine, which is highlighted by the fact that a new pharmacon in this field was also approved in 2024. However, despite the approved drugs with different chemical structures and different mechanisms of action, there is still a large, untapped therapeutic potential in epigenetics, so for example, drugs based on HAT and HDM inhibition are still waiting to be developed.

Acknowledgements

Supported by the University of Debrecen Scientific Research Bridging Fund (DETKA).

Data Availability Statement:

All measurement data are available at the corresponding author in case of further requests.

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