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Recent Advances in Structural Aspects of Small Molecules as Epigenetic Inhibitors in Cancer Therapeutics

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Abstract

Cancer is a non-contagious disease whose treatment poses considerable difficulty for the worldwide healthcare system, even though numerous pharmacological and therapeutic advancements have been achieved. Although cancer rates are going up, survival rates have also improved in many cases, largely thanks to better and more specific drugs. These new drugs target specific changes in tumors, which are identified molecular testing. These changes can be in the deoxyribonucleic acid (DNA) sequence, or in the 'epigenetics', which does not change the DNA sequence. Importantly epigenetic changes can be reversed, unlike DNA changes. Different types of epigenetic enzymes which target corresponding protein domains, emphasize DNA methylation, histone modifications, and microRNA-mediated cooperation with epigenetic modification, and highlight recent achievements in developing targets for epigenetic inhibitor therapy. This article reviews current anticancer small-molecule inhibitors targeting epigenetic modified enzymes and displays their performances in different stages of clinical trials.

Keywords

Epigenetics, Small molecules, Cancer, DNA Methyltransferase Inhibitors, Histone

1. Introduction

The importance of small compounds as epigenetic inhibitors has been brought to light by recent developments in cancer

treatments. Histone alterations and DNA methylation are two examples of epigenetic changes that are crucial to the initiation and spread of cancer. [1]. Because of their reversible nature, these alterations are ideal candidates for therapeutic intervention. Small molecule inhibitors that target epigenetic enzymes have demonstrated encouraging outcomes in preclinical and clinical settings, providing a new avenue for the therapy of cancer [2]. Cancer is characterized by epigenetic dysregulation, which involves enzymes such as histone methyltransferases (HMTs) including EZH2 and DOT1L, DNA methyltransferases (DNMTs), and histone deacetylases (HDACs). In order to reduce tumor growth and restore normal epigenetic patterns, small molecule inhibitors that target these enzymes have been produced. HDAC inhibitors like vorinostat and DNMT inhibitors like azanucleosides, for example, have been authorized for clinical usage, especially in hematological malignancies [3]. Furthermore, combining epigenetic medications with other treatments like immunotherapy and targeted therapy has demonstrated promise in reducing tumor resistance and improving the effectiveness of treatment. This review aims to explore the structural aspects of small molecules as epigenetic inhibitors in cancer therapeutics, focusing on their design, mechanism of action, and recent clinical advancements [4]. It will also discuss the challenges and future directions in the development of these inhibitors as effective cancer treatments.

2. Epigenetic Modifications and Human Diseases

Epigenetic modifications are important in regulating gene expression which does not change the underlying DNA sequencing. Numerous biological processes, including cell differentiation, replication, and development, depend on these alterations, which include histone modifications, DNA methylation, chromatin remodeling, and noncoding RNA regulation [5]. The etiology and progression of many diseases, including cancer, metabolic disorders, neurological ailments, and cardiovascular diseases, have been linked to epigenetics. Because epigenetic modifications are reversible, therapeutic approaches find them to be appealing targets. Comprehending these alterations is crucial for creating innovative diagnostic instruments and therapies. Recent studies have highlighted the merit of epigenetic biomarkers and drugs in managing diseases like diabetes, obesity, and cancer [6]. However, epigenetic interventions also carry risks of unintended consequences, emphasizing the need for rigorous research to ensure safe and effective therapies. This review aims to explore the relationship between epigenetic modifications and human diseases, focusing on the mechanisms by which epigenetic changes influence disease susceptibility and progression. It will also discuss recent advances in epigenetic therapies and their potential applications in clinical settings [7].

3. Epigenetics and Cancer

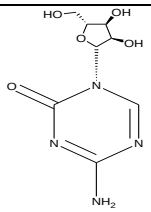
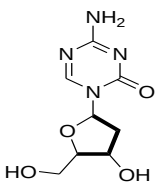
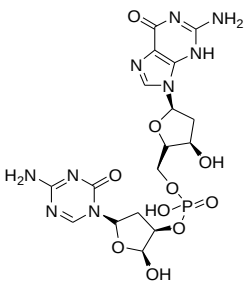
It is becoming more well acknowledged that both genetic and epigenetic changes can impact cancer. Because they change gene expression without modifying the DNA sequence itself, epigenetic alterations such as histone modifications, DNA methylation, and noncoding RNA expressions—are important in carcinogenesis. Through the interplay of oncogenes and tumor suppressor genes, epigenetic and genetic alterations lead to carcinogenesis and metastasis [8]. Without altering the genome's sequence, epigenetic alterations controlled the expression of certain genes. Tumor formation and progression may be aided by these alterations, which may result in the activation of oncogenes and the silencing of tumor suppressor genes. Because epigenetic modifications can be reversed, they are desirable targets for cancer treatment. In therapeutic contexts, epigenetic medicines, such as histone deacetylase inhibitors (HDACis) and DNA methyltransferase inhibitors (DNMTis), have demonstrated promise either alone or in conjunction with other treatments. Recent developments in our knowledge of epi-genetic reprogramming in cancer emphasize how it helps cancer cells become more resistant to drugs and capable of self-renewal by fostering a stem-like state [9]. The development of tailored precision medicine strategies to enhance cancer diagnosis and treatment results requires the combination of genetic and epigenetic data.

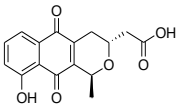
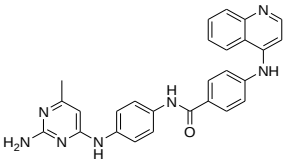
3.1. DNA Methylation

One essential epigenetic mechanism that is important for controlling gene expression and maintaining genomic stability is DNA methylation. One of the hallmarks of cancer is abnormal DNA methylation patterns, which help to activate oncogenes and silence tumor suppressor genes. [10] While hypomethylation can activate proto-oncogenes and retrotransposons, causing genomic instability and the advancement of cancer, hypermethylation of promoter regions usually results in the transcriptional silence of genes. The formation of partially methylated domains (PMDs), which are sizable areas with intermediate methylation levels that change the general structure of heterochromatin and nuclear organization, is one aspect of the com-plex landscape of DNA methylation in cancer that has been brought to light by recent investigations. In addition to providing possible therapeutic targets for cancer treatment, DNA methylation alterations can be useful indicators for early cancer identification and prognosis. [11] Nonetheless, a major obstacle in the research is still the creation of targeted treatments that may specifically undo damaging methylation patterns without having negative side effects. These findings highlight the tremendous potential of genome methylation anomalies in carcinogenesis and provide insight into cancer detection and treatment [12].

Table 1. List of DNA methyltransferase inhibitors under different phases of clinical trial and their indication

DNA methyltransferase inhibitors

Classification	Compound	Structure	Clinical Stage
Nucleoside analogue	Azacytidine		Phase III
	Decitabine		Phase II
	SGI-110		Phase II

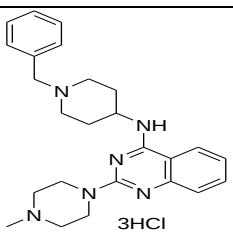
Nonnucleoside analogue	Nanaomycin A		Preclinical
	SGI-1027		Preclinical
	MG98	uncovered	Phase II

3.2. Covalent Histone Modifications

Covalent histone modifications are critical regulators of chromatin structure and function, significantly influencing gene ex pression and cellular identity in cancer. Acetylation, methylation, phosphorylation, and ubiquitination are among the alterations that are mediated by certain enzymes referred to as "writers," "erasers," and "readers." These changes interact dynamically to form the "histone code," a sophisticated regulatory framework that controls a number of biological functions, including transcription, DNA replication, and repair. [13] Histone modification dysregulation has been increasingly associated with carcinogenesis, with abnormal patterns helping to activate oncogenes and silence tumor suppressor genes. For example, leukemia and solid tumors have been linked to changes in methylation marks, specifically at lysines 4 and 27 on histone H3 (H3K4 and H3K27). According to recent research, miswriting or misinterpreting these histone marks may cause dysregulated gene expression and encourage the development, spread, and metastasis of tumors. Therefore, a possible therapeutic approach for the therapy of cancer is to target the enzymes that cause these alterations. [14] The discovery of small molecule inhibitors that modulate histone acetylation and methylation is currently being explored to restore normal epigenetic states in cancer cells, highlighting the potential of epigenetic therapies as a novel approach in oncology. In physiological and pathological processes, miRNAs essentially control epigenetic modifier enzymes, which create a trilateral regulatory "epi–miR–epi" feedback loop. A new hypothesis of gene regulation resulting from this "epi–miR–epi" relationship may aid in the development of novel cancer chemotherapeutics and a deeper understanding of human cancer genesis [15].

Table 2. A list of histone lysine methyltransferase inhibitors under different phases of clinical trial and their indication.

Histone lysine methyltransferase inhibitors

Classification	Compound	Structure	Clinical Stage
G9a (H3K9)	BIX-01294		Preclinical

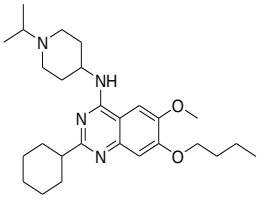
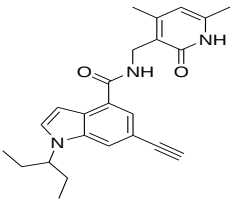
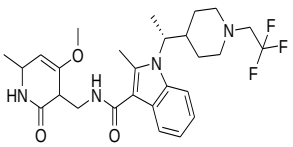
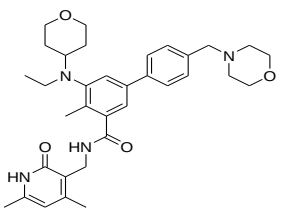
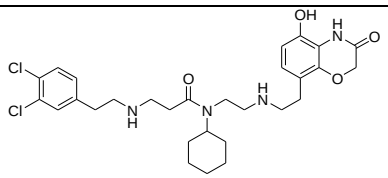
	UNC0638		Preclinical
EZH2 (H3K27)	B1		Preclinical
	CPI-1205		clinical
	EPZ6438		clinical

Table 3. (Continued) A list of histone lysine methyltransferase inhibitors under different phases of clinical trial and their indication.

Histone lysine methyltransferase inhibitors

Classification	Compound	Structure	Clinical Stage
SMYD2	(H3K36) AZ-505		Preclinical

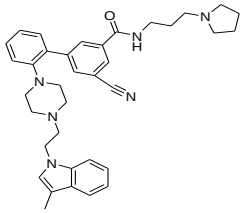
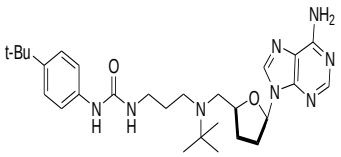
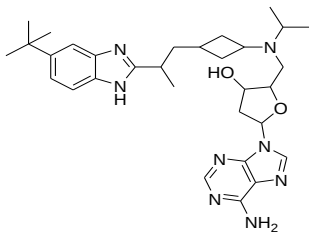
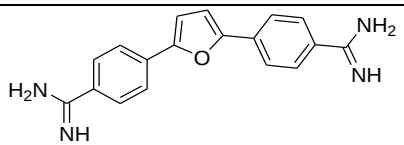
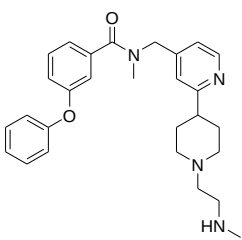
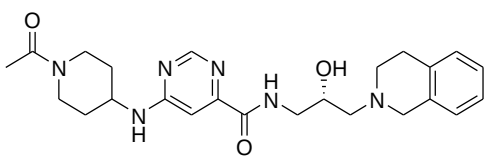
	LLY-507		Preclinical
DOT1L	(H3K79) SYC-522		Preclinical
	EPZ-5676		clinical

Table 4. A list of histone arginine methyltransferase inhibitors under different phases of clinical trial and their indication.

Histone arginine methyltransferase inhibitor

Classification	Compound	Structure	Clinical Stage
PRMT1 DB75	DB75		Preclinical
PRMT4	TP064		Preclinical
PRMT5	EPZ015938 (GSK3326595)		Clinical

4. Epigenetic Therapy of Cancer

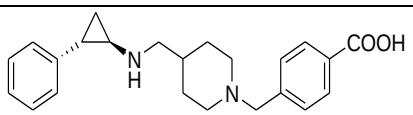
By using the reversible nature of epigenetic changes to restore normal gene expression patterns that were disturbed during tumor formation, epigenetic therapy has become a promising approach to the treatment of cancer. This strategy mainly targets important epigenetic processes that are frequently changed in malignant cells, such as DNA methylation and histone modification. Notably, two well-researched types of epigenetic medications, DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), have shown great promise by reactivating tumor suppressor genes that have been repressed and increasing the expression of genes related to immune responses. Recent studies have shown that clinical results can be significantly enhanced by combining epigenetic therapies with conventional medications like immunotherapy and chemotherapy. [16] For example, DNMT inhibitors can enhance the expression of major histocompatibility complex (MHC) molecules, promoting T-cell penetration into tumor tissues and thereby strengthening the impact of immune checkpoint therapies. However, differences in tumor biology and individual patient responses continue to present obstacles in fine-tuning these therapeutic approaches. Current studies are focused on improving therapeutic strategies, identifying predictive biomarkers for personalized treatment, and developing novel drug combinations to enhance efficacy while reducing side effects.[17] As our understanding of cancer epigenetics deepens, epigenetic therapy holds considerable promise for advancing precision oncology and improving patient prognoses. Several small-molecule inhibitors that regulate chromatin structure have already reached advanced clinical trial phases, and the U.S. Food and Drug Administration (FDA) has approved agents such as fedratinib (a JAK2 inhibitor), vorinostat (an HDAC inhibitor), and others targeting DNMTs for clinical use.

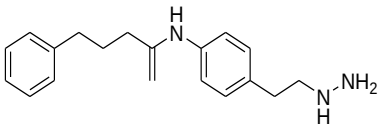
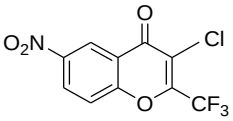
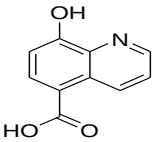
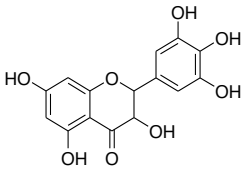
4.1. DNA Methyltransferase Inhibitors

DNA methyltransferase inhibitors (DNMTis) are emerging as pivotal agents in cancer therapy by targeting aberrant DNA methylation patterns that silence tumor suppressor genes and promote oncogenesis. As nucleoside analogs, these inhibi-tors—like 5-azacitidine and decitabine integrate into DNA during replication and create permanent connections with DNMT enzymes, especially DNMT1 and DNMT3A/B, which cause the enzymes to degrade and thus cause DNA hypomethylation. [18] By upregulating major histocompatibility complex I (MHC-I) and cancer-testis antigens, this reactivation of repressed genes improves tumor immunogenicity by enhancing the ability of natural killer (NK) cells and cytotoxic T lymphocytes (CTL) to recognize cancer cells. Clinically, DNMTis are FDA-approved for hematological malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), where they show promise in lowering tumor growth and enhancing survival. Recent studies also high light their potential in solid tumors and synergistic effects when combined with immunotherapy or histone deacetylase inhibitors, amplifying anti-tumor immune responses.[19] However, challenges such as transient efficacy, toxicity, and resistance mechanisms underscore the need for optimized dosing strategies and novel non-nucleoside inhibitors. Ongoing research focuses on epigenetic remodeling to reverse oncogenic gene silencing while minimizing off-target effects, positioning DNMT is as a cornerstone of evolving epigenetic cancer therapies.[20]

Table 5. A list of histone demethylase inhibitors under different phases of clinical trial and their indication

Histone demethylase inhibitor

Classification	Compound	Structure	Clinical Stage
LSD1 inhibitors	Tranylcypromine analogue (GSK2879552)		Clinical

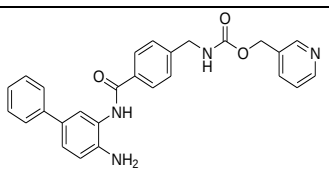
	Bizine		Preclinical
	PG11144		Preclinical
	Namoline		Preclinical
JmjC domain inhibitors	IOX1		Preclinical
	KDM6B		Preclinical

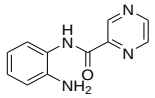
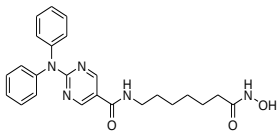
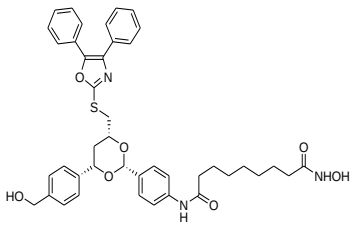
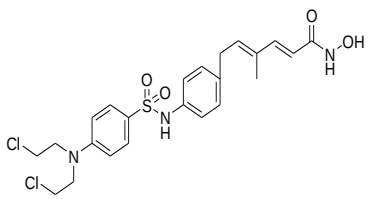
Zebularine functions as a DNA methyltransferase (DNMT) inhibitor in cancer by forming covalent complexes with DNMT enzymes (e.g., DNMT1, DNMT3A/B), trapping them on DNA and preventing methylation. Unlike 5-azacitidine or decitabine, zebularine's pyrimidinone ring lacks a 4-amino group, enabling irreversible binding to the catalytic cysteine residue of DNMTs and subsequent enzyme degradation. While it reduces DNMT protein levels, its anticancer effects in some contexts (e.g., hepatocellular carcinoma HepG2 cells) occur via DNA methylation-independent pathways, including Cell-cycle arrest through p21/p53 upregulation and CDK2/Rb phosphorylation suppression, Apoptosis induction via Bcl-2 down regulation and PKR activation, MAPK pathway modulation, increasing phosphorylated p44/42 to drive growth arrest.[21] In cholangiocarcinoma and other cancers, zebularine induces DNA hypomethylation, reactivating tumor suppressor genes and signaling pathways.

Its oral bioavailability and low cytotoxicity in normal cells enhance therapeutic potential, though efficacy varies by cancer type and dose. Structural studies confirm its covalent DNMT binding mimics enzymatic transition states, disrupting methylation. This dual mechanism epigenetic remodeling and direct signaling modulation positions zebularine as a versatile candidate for combination therapies targeting drug-resistant cancers.[22]

Table 6(a). A list of histone deacetylase inhibitors under different phases of clinical trial and their indication.

Histone acetyltransferase inhibitors

Classification	Compound	Structure	Clinical Stage
HDAC1/2i	MRLB-223		Preclinical

HDAC3i	BG45		Preclinical
HDAC6i	Rocilinostat (ACY-1215)		clinical
	Tubacin		Preclinical
HDAC8i	C1A		Preclinical

In cancer biology, lysine methylation is important, especially when it comes to post-translational changes that control transcription factors. [23] This process, which is carried out by lysine methyltransferases (KMTs), creates different methylation states (mono-, di-, or trimethyl lysine) by adding one to three methyl groups to the ε-amino group of lysine residues. [24] These changes may affect gene expression and aid in the development of tumors by changing the stability and functionality of transcription factors. Because aberrant lysine methylation patterns can activate oncogenes or silence tumor suppressor genes, dysregulation of KMTs has been linked to a number of malignancies. Inhibitors targeting KMTs are being explored as potential anticancer agents, offering a novel therapeutic strategy to reverse aberrant transcriptional activity and inhibit cancer cell proliferation.[25] Recent studies suggest that disrupting lysine methylation can effectively reverse tumor progression both in vitro and in vivo, underscoring its clinical relevance in cancer therapy. These discoveries could lead to novel therapies that target these epigenetic changes particularly as studies into the complexity of lysine methylation in cancer continue. [26] Histone methylation is an important epigenetic alteration that affects chromatin structure and gene expression, especially in cancer. DNA methyltransferase inhibitors (DNMTis), like decitabine and 5-azacitidine, affect histone alterations in addition to inhibiting DNA methylation. [27] For example, 5-azacitidine therapy has been linked to increased trimethylation of lysine-4 on histone H3 (H3K4me3), which is linked to active transcription and the reactivation of tumor suppressor genes that had been silenced. Because it can promote the transcription of previously silenced genes and reverse the tumorigenic phenotype in cancer cells, this interaction between DNA and histone methylation is important. [28]

Furthermore, the inhibition of DNMTs can indirectly affect histone methylation patterns. For example, the DNMTi guadecitabine has been shown to induce tri-methylation of lysine-27 on histone H3 (H3K27me3) when combined with histone deacetylase inhibitors, enhancing gene expression and potentially improving patient outcomes in triple-negative breast cancer. [29] In addition to highlighting the possibility for combinatorial therapies that target both DNMTs and histone methyl-

transferases to create more successful therapeutic techniques, this interplay between DNA methylation and histone alterations shows the intricacy of epigenetic control in cancer.

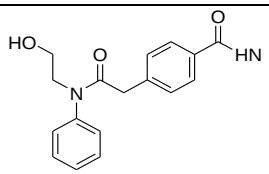
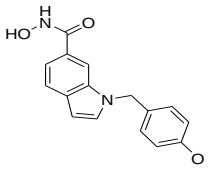
One important epigenetic alteration that greatly affects chromatin dynamics and gene expression, especially in the context of cancer, is histone lysine methylation. Histone lysine methyltransferases (HKMTs) catalyze the methylation of histones on their lysine residues by transferring methyl groups from S-adenosylmethionine (SAM) to certain lysines, resulting in mono, di, or trimethylated forms. Depending on where they occur, these changes can either activate or repress transcription. For instance, H3K4 methylation is typically linked to active transcription, but H3K27 methylation is linked to transcriptional repression. [30]

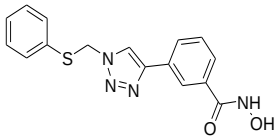
In the realm of cancer therapy, DNA methyltransferase inhibitors (DNMTis) not only target DNA methylation but also impact histone lysine methylation patterns. For example, it has been demonstrated that DNMTs such as decitabine change histone modifications, which reactivates tumor suppressor genes that had been silenced. By restoring normal gene expression profiles, this interaction between DNA and histone methylation can improve the effectiveness of cancer treatments. Furthermore, the development of selective inhibitors targeting specific HKMTs, such as EZH2 inhibitors like tazemetostat, highlights the therapeutic potential of modulating histone lysine methylation in cancer treatment. These advancements suggest that combining DNMTis with HKMT inhibitors could provide a synergistic approach to overcoming resistance and improving outcomes in cancer therapy. A family of enzymes known as protein arginine methyltransferases (PRMTs) catalyzes the methylation of arginine residues on proteins. They are essential for a number of biological functions, including as signal transmission, DNA repair, and the control of gene expression. [31] Based on the methylation products they produce, the nine known PRMTs in mammals are divided into three types: Mono methyl arginine (MMA) and asymmetric dimethylarginine (ADMA) are produced by Type I PRMTs (e.g., PRMT1, PRMT3), whereas symmetric dimethylarginine (SDMA) and MMA are produced by Type II PRMTs (e.g., PRMT5). [32]

PRMTs modify histones and other non-histone proteins, influencing chromatin structure and transcriptional activity. For instance, PRMT1 is known to asymmetrically dimethylate histone H4 at arginine 3 (H4R3me2a), an indicator of ongoing transcription. This modification enhances the recruitment of transcriptional machinery and is crucial for gene activation. In contrast, modifications like H4R3me2s, generated by PRMT5, are linked to transcriptional repression.[33]

Table 6(b). (Continued) A list of histone deacetylase inhibitors under different phases of clinical trial and their indication.

Histone acetyltransferase inhibitors

Classification	Compound	Structure	Clinical Stage
	HPOB		Preclinical
	PCI-34051		Preclinical

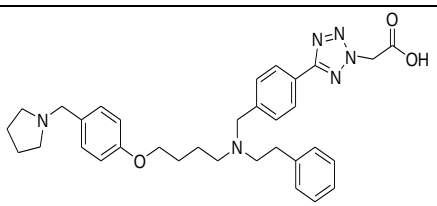
	C149		Preclinical

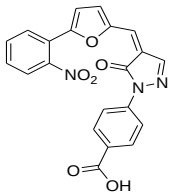
DNA methyltransferase inhibitors (DNMTis) and their effects on cancer treatment are intimately related, because acetylation is a key factor in the control of gene expression. Histone acetyltransferases (HATs) catalyze histone acetylation, which relaxes the chromatin structure and makes it easier for transcriptional machinery to access it. This promotes the expression of genes. In contrast, transcriptional repression and chromatin condensation are the outcomes of histone deacetylation, which is mediated by histone deacetylases (HDACs). [34]

Studies have shown that DNMT inhibitors like 5-azacitidine and decitabine not only block DNA methylation but also have an impact on histone acetylation. Similarly, histone deacetylase inhibitors (HDACis) can boost histone acetylation levels, which in turn may trigger DNA demethylation and restore the activity of silenced tumor suppressor genes. This combined effect is thought to result from enhanced histone acetylation attracting chromatin remodeling complexes, which help remove methyl groups from DNA and create a more transcriptionally active chromatin environment. Moreover, the interaction between acetylation and DNMT activity is complex. Acetylation of specific proteins, such as DNMT1, can affect its stability and function. For instance, the acetylation of lysine residues within DNMT1 can disrupt its interaction with stabilizing proteins like USP7, leading to increased degradation of DNMT1 and reduced DNA methylation levels. This interplay highlights the potential for combining DNMTis with HDAC inhibitors as a therapeutic strategy to enhance anti-tumor effects by simultaneously promoting gene reactivation and altering chromatin structure. Therefore, it is essential to comprehend the dynamics of acetylation in relation to DNMT inhibition to create efficacious cancer treatments that target epigenetic changes. [35] Hyperacetylation of proto-oncogenes can occur because of the action of DNA methyltransferase inhibitors (DNMTis), which play a significant role in cancer therapy by reversing aberrant DNA methylation patterns. Silenced genes, including proto-oncogenes that may have been previously hypermethylated, reactivate when DNMTis, such as 5-azacitidine and decitabine, suppress DNA methylation. This reactivation is often accompanied by increased histone acetylation, which enhances chromatin accessibility and promotes transcription.[36]

Table 7. A list of histone acetyltransferase inhibitors under different phases of clinical trial and their indication.

Histone acetyltransferase inhibitors

Classification	Compound	Structure	Clinical Stage
Tip60	TH1834		Preclinical

p300	C646		Preclinical

The hyperacetylation of proto-oncogenes can result in overexpression, contributing to tumorigenesis. For instance, by inhibiting DNMTs, DNMTis can lead to the upregulation of oncogenes like MYC or RAS, which are critical in driving cell proliferation and survival pathways.[37] Furthermore, there is a complex interaction between histone acetylation and DNA methylation while hyperacetylation typically correlates with gene activation, the simultaneous presence of hypermethylated promoters can lead to a paradoxical silencing effect on certain genes.[38]

4.2. Small Molecules Targeting miRNAs

Small-molecule compounds that target microRNAs (miRNAs) have drawn a lot of interest as possible cancer treatments because of their capacity to alter miRNA expression and aid in reestablishing cellular homeostasis. Short, non-coding RNA sequences called miRNAs are important for post-transcriptional gene regulation. [39] They can function as oncogenic factors, or oncomiRs, or tumor suppressors. Dysregulated miRNA expression can promote the development of cancer by interfering with vital biological functions like metastasis, programmed cell death, and cell proliferation. Small compounds provide a therapeutic means of either reactivating the action of beneficial tumor-suppressive miRNAs that have been downregulated or suppressing detrimental, cancer-promoting miRNAs.[40] For instance, certain small molecules, such as diazobenzene derivatives, have demonstrated the ability to suppress oncogenic miRNAs like miR-21 a critical player in multiple cancer types thereby inhibiting tumor development. Likewise, agents with hypomethylating activity, such as decitabine, can help restore the expression of tumor suppressive miRNAs by demethylating their promoter regions. Advances in computational modeling and high-throughput screening techniques have further accelerated the identification of small molecules capable of selectively targeting specific miRNAs, including inhibitors of miR-122, which plays a significant role in the progression of hepatocellular carcinoma.[41] These molecules act through diverse mechanisms, including direct binding to miRNA precursors or their associated proteins, modulation of transcription factors regulating miRNA expression, or altering epigenetic landscapes.

Despite their promise, challenges such as off-target effects, drug resistance, and delivery remain significant hurdles. Combining small-molecule miRNA modulators with other therapies, such as immunotherapy or epigenetic drugs, offers a synergistic approach to enhance efficacy and overcome resistance. As research progresses, small molecules targeting miRNAs are poised to become integral components of precision oncology.[42]

4.3. Epigenetic Therapy (EpiDrugs) in Acquired Chemoresistance

Epigenetic therapy, often referred to as "EpiDrugs," has emerged as a promising approach to combat acquired chemo-resistance in cancer treatments. Acquired chemoresistance poses a significant challenge in oncology, where tumor cells adapt to evade the effects of chemotherapeutic agents, leading to treatment failure and disease progression. The epigenetic changes underlying these resistance mechanisms are the focus of epiDrugs, such as histone deacetylase inhibitors (HDACis) and DNA methyl transferase inhibitors (DNMTis). [43]

Epigenetic changes, including DNA methylation and histone modifications, have been shown to be important in controlling gene expression and affecting how tumor cells react to chemotherapy. [44] For example, DNMTis can restore the expression of tumor suppressor genes and improve chemosensitivity by reversing the hypermethylation of these genes. Studies

have shown that combining DNMTis with traditional chemotherapeutics can effectively resensitize resistant cancer cells by modifying their epigenetic landscape. For example, the DNMTi 5-azacytidine has been reported to reverse cisplatin resistance in bladder cancer by demethylating the HOXA9 gene promoter.[45] Moreover, the integration of EpiDrugs with immunotherapies has shown promising results in clinical trials, boosting immune responses against tumors and promoting patient outcomes. Trials combining DNMTis with immune checkpoint inhibitors have indicated increased expression of tumor-associated antigens and improved T-cell infiltration in tumors. This implies that EpiDrugs improve the effectiveness of other therapeutic methods in addition to targeting the innate resistance mechanisms of cancer cells. [46]

Overall, the application of epigenetic therapies offers a novel strategy to overcome acquired chemoresistance by focusing on how epigenetic changes are reversible. As ongoing research continues to elucidate the complex interplay between epi genetics and chemotherapy response, EpiDrugs are poised to play a pivotal role in future cancer treatment regimens, potentially leading to more effective and personalized therapeutic approaches. [47]

5. Conclusion

Our knowledge of small compounds' potential as cancer treatments has greatly increased as a result of recent developments in their structural characteristics as epigenetic inhibitors. These tiny chemicals target a variety of epigenetic changes that are essential for controlling gene expression and preserving cellular homeostasis, such as DNA methylation and histone modifications. Inhibitors of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) have demonstrated promise in correcting the epigenetic changes linked to carcinogenesis. [48]

Structural studies have elucidated the binding mechanisms of these small molecules, revealing how they interact with their targets at the molecular level. The potential of bromodomain and extra terminal domain (BET) inhibitors, for instance, to interfere with the interaction between BET proteins and acetylated lysines and hence prevent oncogenic transcription has been demonstrated by their structural characterization. Additionally, advancements in the design of selective inhibitors for histone methyltransferases (KMTs) and demethylases (KDMs) have provided insights into their specificity and efficacy against various cancer types. The combination of structural biology with high-throughput screening has accelerated the discovery of novel small molecules that can selectively modulate epigenetic targets.[49] This method reduces off-target effects while simultaneously improving the therapeutic index, a common challenge in cancer treatment. Furthermore, the integration of epigenetic inhibitors with other therapeutic modalities, such as immunotherapy and conventional chemotherapy, has demonstrated synergistic effects, leading to improved clinical outcomes. The structural features of tiny compounds as epigenetic inhibitors are still being studied, and this research has enormous potential for creating more potent cancer treatments. These drugs can overcome medication resistance and restore normal gene expression patterns by focusing on the reversible nature of epigenetic modifications. This opens the door for novel treatment approaches that improve patient survival and quality of life.

6. References

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