

An Overview of STING as an Anticancer Target: Structure, Function, and Inhibitors

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Abstract

The cGAS-STING pathway serves as a critical signaling axis for cytoplasmic DNA sensing and innate immune activation. As a central adapter protein, STING (Stimulator of Interferon Genes) plays a pivotal role in tumor immune surveillance, inflammatory responses, and the pathogenesis of various diseases. This article reviews the molecular architecture, functional domains, and signaling mechanisms of STING, while addressing the impact of genetic polymorphisms and interspecies variations. We elucidate the dual regulatory role of STING in tumorigenesis, where moderate activation facilitates antitumor immunity, whereas chronic overactivation or inactivation paradoxically promotes tumor progression. Furthermore, we explore the link between aberrant STING signaling and immune evasion. Finally, We have classified STING inhibitors into four major categories: covalent inhibitors targeting Cys91, inhibitors that competitively bind to the CDN-binding pocket, inhibitors that block oligomerization, and inhibitors acting via other mechanisms; furthermore, we have summarized their binding sites, molecular mechanisms, representative compounds, and current research status. This review provides a comprehensive theoretical framework for advancing basic research on the STING pathway, targeted drug design, and precision medicine.

Keywords

STING, cGAS-STING, Pathway, Tumor, Inhibitor, Targeted Therapy

1. Introduction

The innate immune system recognizes cytoplasmic abnormal DNA through PRRs

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(Pattern Recognition Receptors), thereby initiating host defense, inflammatory responses, and immune surveillance. It serves as a critical line of defense against pathogen infections, cellular damage, and tumorigenesis. As the central signaling axis for cytoplasmic DNA sensing, the cGAS-STING pathway plays an irreplaceable pivotal role in innate immune activation, the initiation of adaptive immunity, and the pathological processes of various diseases [1] [2]. STING, as the central adapter protein of this pathway, is activated by 2'3'-cGAMP (Cyclic GM-AMP) produced by cGAS (Cyclic GMP-AMP Synthase) [3]. Through conformational changes, Golgi translocation, Cys91 palmitoylation, and oligomerization, it recruits TBK1 (TANK-binding kinase 1) and activates IRF3 (Interferon Regulator Factor 3) and NF- κ B (Nuclear Factor kappa-light-chain-enhancer of activated B cells), thereby inducing the expression of type I interferons and pro-inflammatory factors. The elucidation of STING's structure and key functional domains provides a solid structural foundation for the development of small-molecule drugs targeting STING. Multiple functional genetic polymorphisms of STING exist in the population, with subtypes such as R232H, H239Y, R71H, and HAQ (R71H-G230A-R293Q) being the most common. Among these, R232H is the most prevalent subtype globally; it directly alters the conformation of the ligand-binding pocket [4], affecting CDN (cyclic dinucleotide) binding capacity and activation efficiency. The HAQ variant [5] has a carrier frequency as high as 31% in East Asian populations; as a typical loss-of-function allele, it significantly reduces type I interferon induction capacity, directly leading to individual differences in response to targeted drugs. Furthermore, inherent differences in the key amino acid sequences of the ligand-binding pocket between human and mouse STING result in significant species-specificity among many small-molecule agonists and inhibitors, posing a major constraint on the translation of preclinical research into clinical applications.

In the field of oncology, the STING pathway exhibits strict background-dependent dual regulatory effects that are critically distinguished by the duration and intensity of activation. Moderate acute activation can drive the transformation of “cold tumors” into “hot tumors,” enhance CD8⁺ T cell and NK (natural killer cells) cell infiltration, and exert an anti-tumor immune surveillance effect [6] [7]. This acute signaling axis is therapeutically desirable in immunologically “cold” solid tumors, where restoring STING activity reactivates immune surveillance; consequently, STING agonists are preferentially indicated in these settings, particularly in combination with PD-1/PD-L1 inhibitors. Conversely, pathway inactivation or chronic overactivation mediates immune suppression, tumor invasion and metastasis, and immune evasion. Both extremes (chronic hyperactivation and functional inactivation) create a tumor-permissive microenvironment; under these pathological conditions, STING inhibitors are the preferred therapeutic modality to restore immune homeostasis or suppress pro-tumorigenic inflammation. Additionally, abnormal STING activation is closely associated with SAVI (STING-Associated Vasculopathy with Onset in Infancy), AGS (Aicardi-Goutières Syndrome), systemic lupus erythematosus, organ fibrosis, and neurodegenerative diseases, mak-

ing STING a key target for interventions in inflammation and cancer [8]-[10].

Although STING agonists have entered multiple clinical trials for cancer, the systemic inflammation, autoimmune damage, and tumor-promoting effects in certain tumors caused by STING overactivation have led to increasing attention on the development of STING inhibitors. This review therefore focuses on elucidating the molecular basis of STING inhibition, while maintaining a clear conceptual distinction between the acute antitumor benefits of transient STING activation and the therapeutic rationale for STING suppression in chronic or dysregulated signaling contexts. Currently, inhibitors targeting the ligand-binding pocket, the Cys91 palmitoylation site, and the oligomerization interface have been reported, with some compounds demonstrating promising *in vitro* and *in vivo* activity as well as potential for clinical translation. However, STING inhibitors still face challenges such as species specificity, resistance in mutant forms, oral bioavailability, and insufficient selectivity. This article provides a systematic review of STING's molecular structure, biological functions, and inhibitor binding pocket characteristics, with a focus on the association between STING and tumorigenesis and progression, as well as the classification, mechanisms of action, and research progress of STING inhibitors. The aim is to provide a comprehensive theoretical reference for basic research on the STING pathway, targeted drug design, and the treatment of tumor- related and inflammation-related diseases.

1.1. Structure of STING

STING, also known as TMEM173 (Transmembrane Protein 173), MITA (Mediator of IRF3 Activation), ERIS (Endoplasmic Reticulum Interferon Stimulator), or MPYS (Mediator of Pyrogenic Response), is a transmembrane protein localized to the endoplasmic reticulum and encoded by the TMEM173 gene. Mouse and human STING exhibit high sequence homology and highly conserved domain features. The human STING protein consists of 379 amino acids [11]-[13]. As shown in **Figure 1(a)**, the STING protein can be clearly divided into three functionally specialized regions: the N-terminal transmembrane domain, the cytoplasmic linker domain, and the CTD (C-terminal domain). These domains act in concert to collectively mediate the entire process of STING's subcellular localization, conformational changes, ligand recognition, and downstream signal transduction [14] [15]. The N-terminal transmembrane region contains four transmembrane helices (TM1: residues 18 - 34; TM2: 45 - 69; TM3: 92 - 106; TM4: 117 - 134), which are responsible for firmly anchoring the STING protein to the endoplasmic reticulum membrane and serve as the key structural foundation for maintaining its subcellular localization; simultaneously, this domain also participates in the initiation of STING protein dimerization, providing the necessary spatial conformation support for its subsequent activation. TM2 and TM3 are connected by two linker peptides (TM2-TM3 linker), which constitute the key region for conformational changes. Upon recognition of cytoplasmic DNA, this region mediates the transport of the STING protein from the endoplasmic reticulum through the ER-GIC (endoplasmic reticulum-Golgi intermediate compartment) to the Golgi ap-

paratus, thereby initiating the activation of downstream signaling pathways [16] [17]. The CTD encompasses the LBD (ligand-binding domain), the IRF3-binding domain, and the TBM (TBK1-binding motif). Within the CTD, hydrophobic interactions form a homodimer, creating a conserved V-shaped ligand-binding pocket that specifically recognizes CDNs (cyclic dinucleotides, such as 2'3'-cGAMP); the C-terminal tail contains a TBK1 phosphorylation site responsible for signal transduction [18] [19]. **Figure 1(b)** shows that STING exists as a V-shaped homodimer, with four N-terminal transmembrane helices embedded in the membrane. The connector helix extends outward, serving as a bridge between the transmembrane region and the CTD. The TM2-TM3 connecting peptide forms a ring structure at the interface of the dimer, while the CTD protrudes outward to form the ligand-binding pocket. Notably, Cys91 in the transmembrane region is a key palmitoylation site, which is crucial for STING oligomerization and downstream signal activation. Additionally, human STING has natural variants such as R232H (located in the CTD) and HAQ (R71H-G230A-R293Q); these mutations alter CDN binding capacity. Among these, HAQ and some R232 subtypes are loss-of-function alleles, while subtle sequence differences in the ligand-binding pocket between murine and human STING result in species-specific responses to many modulators, making this a key consideration in preclinical drug development.

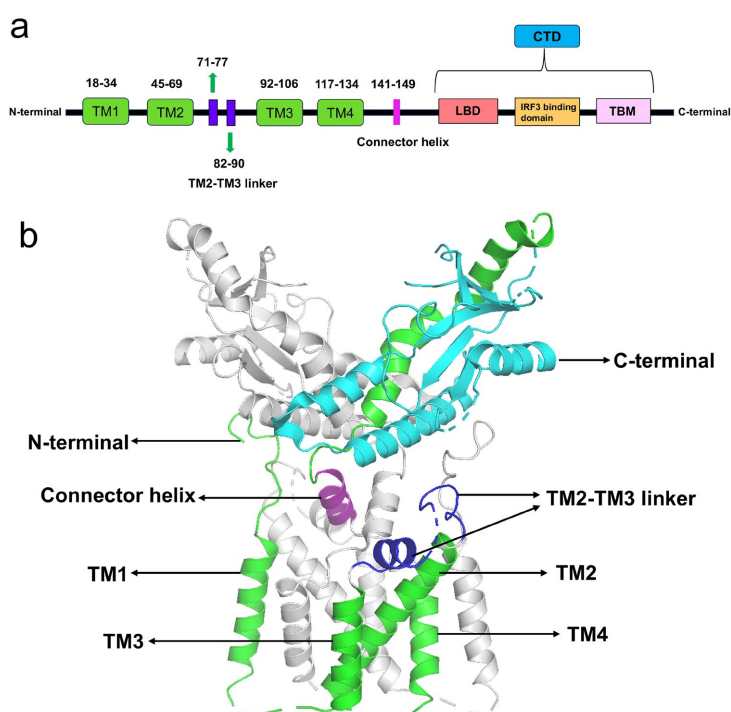


Figure 1. Domain organization and structural model of the protein. (a) Schematic representation of the protein architecture, showing the four trans-membrane helices (TM1-TM4), the TM2-TM3 linker, connector helix, lig-and-binding domain (LBD), IRF3-binding domain, TBM, and C-terminal domain (CTD). Amino acid boundaries of major regions are indicated. (b) Three-dimensional structural model highlighting the spatial arrangement of the transmembrane helices, TM2-TM3 linker, connector helix, and the N- and C-terminal regions.

1.2. Biological Functions of STING

As the central adapter molecule in the cytoplasmic DNA innate immune pathway, STING's core biological function is to mediate the production of type I interferons and pro-inflammatory cytokines triggered by cytoplasmic DNA, thereby initiating and amplifying innate and adaptive immune responses [20]-[22]. As shown in **Figure 2**, activation of this pathway begins with the recognition of dsDNA (double-stranded DNA) within the cytoplasm. DNA derived from pathogens (such as bacteria and DNA viruses), mtDNA (mitochondrial DNA) released from damaged mitochondria, and genomic DNA released from dying or tumor cells can all serve as activation signals. Additionally, RNA viruses can indirectly activate this pathway through the IFN- γ -induced DNA receptor IFI16 (Interferon Gamma Inducible Protein 16) and the DEAD-box helicase DDX41 (DEAD-Box Helicase 41) [23] [24]. cGAS, acting as a cytoplasmic DNA sensor, undergoes a conformational change upon recognizing and binding to dsDNA, catalyzing the conversion of ATP and GTP into the second messenger circular (cGAMP) [25]. cGAMP, as an endogenous ligand, binds to and activates the adapter protein STING on the endoplasmic reticulum membrane. In addition to cGAMP, certain non-canonical CDNs produced by bacteria (such as c-di-GMP, c-di-AMP, and 3',3'-cGAMP) can also directly activate STING. Upon activation, STING undergoes a conformational rearrangement and is transported from the endoplasmic reticulum to

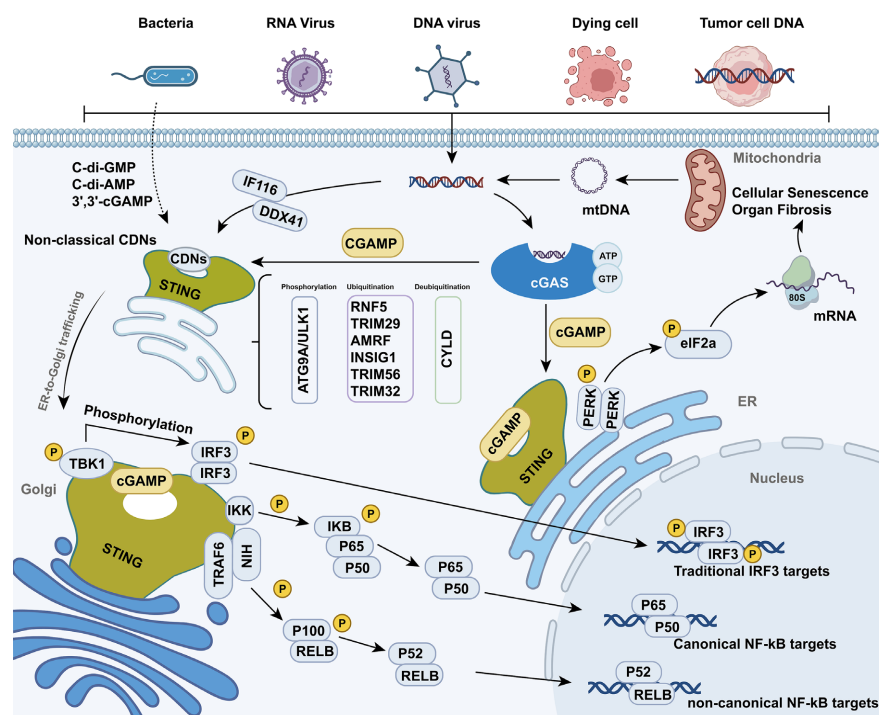


Figure 2. Overview of cGAS-STING signaling and its downstream responses. Cytosolic DNA derived from pathogens or damaged host cells activates cGAS to generate cGAMP, which binds STING and triggers its trafficking and activation. Activated STING induces IRF3 and NF- κ B signaling, translational control through PERK-eIF2 α , and downstream inflammatory, senescence, and fibrosis-related responses.

the Golgi apparatus [26] [27]. During this process, STING recruits and activates TBK1. TBK1 phosphorylates the C-terminal domain of STING, providing a binding site for IRF3, which is subsequently phosphorylated. Activated IRF3 dimerizes and translocates into the nucleus, inducing the expression of type I interferons (such as IFN- β) and ISGs (interferon-stimulated genes) [28] [29]. Concurrently, the STING-TBK1 complex can also activate the NF- κ B pathway by recruiting TRAF6 (TNF Receptor-Associated Factor 6) and NIK (NF- κ B-Inducing Kinase): in the classical pathway, the IKK (I κ B Kinase) phosphorylates I κ B, promoting its degradation and releasing the p65/p50 heterodimer into the nucleus; in the non-classical pathway, NIK activation leads to the processing of p100 into p52, forming a RELB/p52 complex that translocates into the nucleus; these two components regulate the expression of inflammatory factors and anti-apoptotic genes, respectively. Furthermore, this pathway is finely regulated by various post-translational modifications. STING can be ubiquitinated by E3 ubiquitin ligases and can also be regulated by the deubiquitinating enzyme. Phosphorylation affects the transport efficiency of STING. Notably, sustained activation of the STING signaling pathway can also induce the UPR (unfolded protein response) by the PERK-eIF2 α pathway, and even regulate cellular senescence, organ fibrosis, and mRNA translation processes, demonstrating its multifunctionality in physiological and pathological processes [30] [31].

1.3. Inhibitor Binding Pockets

STING, as the central adapter protein in the cGAS/STING cytoplasmic DNA sensing pathway, possesses multiple regions in its molecular structure that can be specifically recognized and bound by small molecules, known as inhibitor-binding pockets. These pockets serve as key functional sites for regulating STING activation and blocking downstream interferon and inflammatory signaling; they also provide a crucial structural foundation for developing targeted drugs to intervene in age-related diseases and tumorigenesis [32]. Based on binding sites, mechanisms of action, and their impact on the STING activation process, currently reported STING inhibitor-binding pockets are primarily classified into three categories: ligand-competitive binding pockets (LBD pockets), palmitoylation modification pockets, and oligomerization interface pockets. These distinct pockets exert regulatory effects at different stages, including ligand recognition, post-translational modification, and oligomer stability. It provides the theoretical basis and molecular targets for the precise targeting of STING.

1.3.1. Ligand-Competitive Binding Pocket (LBD Pocket)

The ligand-competitive binding pocket is located in the C-terminal ligand-binding domain (LBD/CTD) of the STING protein. This is the natural binding site for the endogenous second messenger 2'3'-cGAMP and serves as the core region for STING activation. This pocket is formed by the interface of the STING dimer and can specifically recognize CDN ligands [33]. Ligand binding triggers STING conformational closure and polymerization, thereby activating the TBK1-IRF3 and

NF- κ B signaling pathways. Small-molecule inhibitors designed to block ligand binding are referred to as CDN competitive inhibitors. These compounds directly occupy the LBD pocket, competitively antagonizing the binding of 2'3'-cGAMP to STING, thereby locking STING in an inactive conformation and inhibiting the downstream expression of type I interferons and pro-inflammatory factors. Among them, the sulfonamide derivative SN-011 is a typical LBD pocket-targeting inhibitor that can efficiently bind to the STING ligand-binding domain and block signal activation, serving as an important molecular tool for studying the STING ligand recognition mechanism [34].

1.3.2. Palmitoylation Modification Pocket

The palmitoylation modification pocket is a post-translational modification regulatory pocket essential for STING to achieve Golgi localization and full activation. It is primarily located on the Golgi-facing side of the STING transmembrane domain and is a highly hydrophobic binding region, with the key functional site being Cys91 in human STING. After STING is transported from the endoplasmic reticulum to the Golgi apparatus, palmitoylation of the Cys91 site must occur within this pocket to stabilize the polymeric structure and effectively recruit the downstream TBK1 kinase [35]-[37]; blocking this modification directly terminates STING signaling. Inhibitors targeting this pocket are predominantly covalently binding small molecules that can enter the hydrophobic pocket to modify the Cys91 site or occupy the palmitoylation binding site to inhibit the modification process. Representative inhibitors include the indoleurea compounds H-151, C-176, and C-178, as well as nitrofatty acid and acrylamide derivatives. All of these achieve highly effective inhibition of STING activation by acting on the palmitoylation pocket and have demonstrated significant anti-inflammatory and pathological improvement effects in models of autoimmune inflammation and neurodegenerative diseases.

1.3.3. Oligomerization Interface Pockets

The oligomerization interface is located in the interaction region of STING homodimers and serves as the structural foundation for STING to complete dimerization and further form higher-order active oligomers. Oligomerization is a necessary step in STING signal activation. Among these, the oligomerization interface pocket, as the key functional structure in this region, is located at the interface between the STING dimer and the oligomer [38]. Its core function lies in maintaining the stability of the STING oligomer after activation and mediating the signal amplification process. Although this pocket does not directly participate in the recognition of endogenous ligands, it is crucial for the stability of the STING oligomer and signal amplification following activation. If this oligomerization interface pocket is disrupted, it leads to the disassembly of the activated STING, thereby prematurely terminating the downstream signal transduction process [39] [40]. Small molecules that target the oligomerization interface are defined as STING oligomerization inhibitors, and their core mechanism of action involves

binding to the oligomerization interface to disrupt protein–protein interactions. On one hand, they block the stable assembly of STING dimers and higher-order polymerization processes through steric hindrance or conformational interference, thereby weakening the interaction between STING and TBK1; on the other hand, they can directly inhibit the formation of polymers, achieving a blocking effect at the source of signal transduction. Notably, these inhibitors can precisely regulate the intensity of the STING signaling pathway without affecting ligand binding, providing a novel strategic direction for the treatment of diseases requiring mild and precise inhibition of the STING pathway [41]. In addition to the aforementioned classical inhibition modes, some inhibitors can also target the interaction interfaces between STING and downstream effector molecules such as TBK1 and IRF3. By interfering with protein-protein interactions, they block the phosphorylation of IRF3 and its nuclear translocation. This mechanism constitutes a non-classical mode of STING signaling pathway inhibition.

2. The Relationship between STING and Tumors

The STING pathway, as a central signaling hub of the innate immune system, is primarily responsible for recognizing intracellular abnormal DNA and initiating an immune response. It is closely associated with tumor initiation, progression, and metastasis. The expression levels, activation status, and signaling efficiency of STING in tumor tissues directly regulate the composition of the tumor immune microenvironment and the intensity of the host's antitumor immune response, making it a key regulatory node in tumor immune surveillance and immune evasion. Overall, normal activation of the STING pathway effectively exerts antitumor immune effects and curbs tumor progression; conversely, inactivation, abnormal activation, or dysregulation of the pathway promotes immune evasion by tumor cells and accelerates malignant tumor progression. Furthermore, there is significant heterogeneity in STING expression levels and activation states across tumors of different tissue origins, and the antitumor effects it mediates exhibit distinct tumor-specificity, providing a crucial theoretical basis for stratified tumor therapy.

2.1. STING-Mediated Antitumor Signaling Pathway

During abnormal proliferation, tumor cells continuously release cytoplasmic DNA (including DNA fragments generated by chromosomal instability and mitochondrial DNA) due to pathological events such as genomic instability, mitochondrial damage, and micronucleus fragmentation. Upon recognition by cGAS, this cytoplasmic DNA catalyzes the synthesis of the second messenger 2'3'-cGAMP, which subsequently binds to and activates STING localized in the endoplasmic reticulum. Upon activation, STING undergoes a conformational rearrangement and translocates to the Golgi apparatus, where it undergoes Cys91 palmitoylation and recruits TBK1, which phosphorylates and activates IRF3 and NF- κ B, inducing the transcriptional expression of type I interferons (IFN- α , IFN- β) and pro-in-

flammatory cytokines (IL-6, TNF- α , etc.). This promotes the maturation of dendritic cells and enhances their antigen-presenting capacity, ultimately activating the clonal expansion of CD8⁺ T cells and the formation of tumor immune memory [42].

STING-mediated antitumor effects are achieved through a multi-level immune regulatory network. First, upon activation of the pathway, it induces the secretion of type I interferons, recruiting dendritic cells, macrophages, and NK cells to infiltrate tumor tissues, thereby enhancing the immunological activity of the micro-environment and driving the transformation of “cold tumors” into “hot tumors”; consequently, by activating the antigen-presenting function of dendritic cells, it initiates an adaptive immune response, promotes the clonal expansion of CD8⁺ T cells, and establishes long-lasting tumor immune memory, thereby enabling continuous surveillance and elimination of tumor cells; simultaneously, STING signaling can directly induce immunogenic cell death or apoptosis in tumor cells, inhibiting their proliferation, invasion, and metastatic capacity [43]. Furthermore, the STING pathway exhibits significant synergistic regulatory effects with immune checkpoint pathways such as PD-1/PD-L1 (Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1). STING activation upregulates PD-L1 expression on the surfaces of tumor cells and immune cells, providing a clear target for PD-1/PD-L1 inhibitors; the combined use of these two approaches significantly enhances antitumor efficacy and effectively overcomes immune evasion. Currently, combination therapy with STING agonists and PD-1/PD-L1 inhibitors has entered Phase I/II clinical trials for various solid tumors, including melanoma, non-small cell lung cancer, and bladder cancer, demonstrating promising clinical prospects.

2.2. Differences in STING Expression and Function across Tumor Types

STING expression levels and pathway activity exhibit marked heterogeneity across solid tumors, governed primarily by tissue origin, genetic background, and the tumor immune microenvironment. Based on pan-cancer analyses and the functional status of STING, solid tumors can be stratified into two major phenotypes. The first category comprises tumors characterized by high STING expression and effective pathway activation, including melanoma, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and bladder cancer. In cutaneous melanoma, elevated STING expression is associated with significantly prolonged disease-specific survival [44]. In CRC, both STING mRNA and protein are markedly upregulated in tumor tissues, with increased expression positively correlating with lymph node metastasis [45]. In NSCLC, independent immunohistochemistry cohort studies demonstrate that STING-positive patients exhibit significantly improved median overall survival compared with STING-negative patients [46]. In bladder urothelial carcinoma, cGAS-STING pathway gene expression positively correlates with immune infiltration scores, and tumors with intact cGAS-STING

signaling display chemokine signatures linked to favorable prognosis. Across these malignancies, robust cGAS-STING pathway activation generates substantial type I interferons and pro-inflammatory cytokines, thereby establishing an anti-tumor immune microenvironment dominated by CD8⁺ T cells and dendritic cells [47]. The second category encompasses tumors with low STING expression or inactive signaling pathways, including triple-negative breast cancer (TNBC), prostate cancer, pancreatic cancer, and glioblastoma (GBM) [48]. In breast cancer, ER-positive tumors with low STING expression are associated with poor overall survival, higher tumor grade, and enhanced chromosomal instability. In prostate adenocarcinoma and pancreatic adenocarcinoma, TCGA expression profiling reveals that tumors in the lowest STING expression quartile exhibit significantly attenuated pro-inflammatory gene expression compared with those in the highest quartile [49]. In GBM and other brain tumors, RNA sequencing data indicate wide variation in STING pathway component expression, with advanced-stage pediatric and adolescent/young adult (AYA) gliomas showing decreased overall STING expression relative to primary tumors [50].

Mechanisms underlying STING pathway inactivation in these tumors operate at multiple levels. First, TMEM173 promoter hypermethylation directly silences transcription, as observed in lung adenocarcinoma and lung squamous cell carcinoma. Second, abundant immunosuppressive molecules (IL-10 and TGF- β) within the tumor microenvironment functionally inhibit pathway activation [51]; additionally, in KRAS-mutant NSCLC, LKB1 loss is robustly associated with either complete absence or significant reduction of STING protein levels, representing a genetic mechanism of STING suppression [52] [53]. Third, certain tumor cells degrade STING protein via ubiquitination, or overexpress hydrolases such as ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1) to degrade 2'3'-cGAMP, thereby blocking signal transduction and ultimately leading to STING pathway inactivation. Owing to these STING pathway defects, immune surveillance is severely compromised in such tumors, rendering malignant cells prone to immune evasion and resulting in higher malignancy and poorer prognosis [54].

2.3. Abnormalities in the STING Pathway and Tumor Immune Escape

The inactivation or abnormal regulation of the STING pathway is one of the core mechanisms by which tumor cells achieve immune evasion, involving multiple levels such as gene expression, upstream signaling initiation, signal transduction, and the tumor micro-environment. At the gene and expression levels, high methylation of the TMEM173 gene promoter region frequently occurs in tumor cells, leading to a significant reduction in STING transcription levels. Alternatively, gene deletions or loss-of-function mutations may result in abnormal protein expression, preventing the effective recruitment of TBK1 and the activation of the downstream IRF3/NF- κ B signaling axis. This is a common immune evasion mechanism in colorectal cancer, gastric cancer, and melanoma. At the upstream

signaling initiation level, cGAS acts as a receptor for the pathway, its activity can be abnormally suppressed by tumor cells through various mechanisms, such as protein degradation, promotion of nuclear localization isolation, or inhibition of DNA-binding capacity. This ultimately reduces 2'3'-cGAMP synthesis, blocking the initiation of the STING pathway at its source [55]. At the signal transduction level, 2'3'-cGAMP acts as a key second messenger, and its concentration directly determines the efficiency of STING activation. Some tumor cells highly express hydrolases such as ENPP1 and PDE (Phosphodiesterase), which can rapidly degrade intracellular and extracellular 2'3'-cGAMP, reducing its effective concentration and preventing it from binding to and activating STING, thereby blocking signal transduction in the pathway. In the tumor microenvironment, Regulatory T cells, M2-type tumor-associated macrophages, and myeloid-derived suppressor cells are highly abundant in the tumor microenvironment and secrete immunosuppressive cytokines including IL-10 and TGF- β , which directly inhibit the activation of the STING-TBK1-IRF3 signaling axis. Simultaneously, these cells directly kill or suppress activated CD8⁺ T cells, comprehensively weakening the host's antitumor immune response [56]. In response to the immune evasion mechanisms mediated by abnormalities in the STING pathway described above, therapeutic strategies targeting the STING pathway (such as STING agonists, cGAS activators, and ENPP1 inhibitors) can effectively reverse the tumor-suppressive microenvironment by restoring pathway integrity and signaling capacity, thereby enhancing immune cell infiltration and cytotoxic functions. These approaches have become a highly promising and significant research direction in the field of cancer immunotherapy.

3. STING Inhibitors

In cancer immunotherapy, STING agonists have been the mainstream focus of research. However, excessive activation of the STING pathway can lead to severe immune-related adverse reactions, such as systemic inflammatory responses and autoimmune diseases. Additionally, in certain tumors, abnormal activation of the STING pathway promotes tumor proliferation and metastasis, necessitating the use of STING inhibitors to regulate pathway activity. Although many compounds detailed below were initially characterized in inflammatory or acute kidney injury models, their inhibitory mechanisms are directly applicable to oncology contexts where chronic STING activation drives tumor progression and immune evasion. Among the four major inhibitor classes, competitive CDN-binding pocket inhibitors and covalent Cys91-targeting inhibitors currently offer the most direct translational rationale for cancer therapy. Specifically, competitive CDN-binding pocket inhibitors, represented by SN-011, have advanced into Phase I clinical trials for cancer-associated inflammatory diseases, while covalent Cys91-targeting inhibitors exert antitumor effects by blocking palmitoylation-dependent signaling within the tumor microenvironment. Oligomerization blockers and targeted protein degraders, although preclinically validated primarily in autoinflammatory

disease models, possess distinct strategic advantages in overcoming mutant resistance and achieving sustained pathway ablation, suggesting expanding utility in genetically heterogeneous or STING-driven tumors. Currently identified STING inhibitors can be classified into four major categories based on their binding sites and mechanisms of action. Each class possesses unique chemical structures and functional characteristics, and some inhibitors have already entered the preclinical research phase, offering new approaches to addressing immune-related issues in cancer therapy.

3.1. Covalent Cys91-Targeting Inhibitors

Covalent Cys91-targeting inhibitors block palmitoylation by forming a stable covalent bond with the Cys91 residue (Cys88 in Raw) of the human STING protein, thereby inhibiting STING's transport from the Golgi apparatus, its oligomerization, and downstream signal activation. This represents the most well-established irreversible inhibition strategy to date. Overall, representative compounds in this class predominantly exhibit preclinical efficacy in murine inflammatory and kidney-injury models, with select members (H-151, C-171, compound 3b, and compound 66) demonstrating dual human/Raw inhibitory activity. However, sensitivity to prevalent human variants (such as R232H or HAQ) and clinical-stage translation remain largely unexplored. Compared to other types of STING inhibitors, covalent Cys91-targeting inhibitors offer significant advantages, including strong *in vivo* activity and prolonged duration of action. They have become the most widely used STING inhibition strategy and show great promise in the treatment and research of various diseases, including autoimmune diseases, neuroinflammation, and cancer. **Figure 3** and **Figure 4** summarize covalent STING inhibitors targeting Cys91 and their inhibitory activities. This class of inhibitors is represented by indole-urea scaffolds, with H-151 serving as a classic tool compound that exhibits both human and murine inhibitory activity. It has demonstrated good therapeutic effects in various disease models, including systemic lupus erythematosus, autoinflammatory diseases, amyotrophic lateral sclerosis, and neuroinflammation; QQ21, derived from this scaffold, has an IC_{50} (Half Maximal Inhibitory Concentration) of 86 nM in murine cells, exhibiting 8-fold higher activity than H-151. It directly binds to STING and significantly inhibits downstream signaling pathways, demonstrating potent *in vivo* anti-inflammatory activity in both CMA-induced inflammation and cisplatin-induced acute kidney injury models [57]. Compound 42 (IC_{50} =7.1 nM, Raw) blocks STING palmitoylation, exhibits excellent oral bioavailability (15.0%) and *in vivo* safety, and demonstrates superior inhibitory activity, effectively suppressing inflammatory responses [58]. Compound 66, based on H-151, was structurally optimized by targeting metabolic hotspots. It was found to have IC_{50} values of 116 nM and 96.3 nM against human and mouse STING, respectively, with an oral bioavailability of 12.7%, and demonstrated effective anti-inflammatory activity in an acute kidney injury model [59]. Chang *et al.* used H-151 as a lead compound to study indole-phenylaminocarbamide STING inhibitors and found that compound 21 [60] exhibited

the highest activity. Molecular docking and molecular dynamics simulations confirmed that its binding site is close to the Cys91 residue of STING and identified key structure-activity relationships. The nitrofuran/indole series includes compounds C-170, C-176, C-178, and C-171. Among these, C-176 exhibits excellent blood-brain barrier permeability, while C-171 addresses species-specific issues and possesses dual inhibitory activity against both human and mouse STING, making it the preferred choice for cross-species research. Compound Y2 and Compound HY2 were obtained by structurally optimizing C-170 and H-151 via a hydroxyl insertion strategy [61]. Both compounds effectively inhibit STING pathway activation and demonstrate significant anti-inflammatory and nephroprotective effects in a mouse model of cisplatin-induced acute kidney injury, showing potential for further development as anti-inflammatory drugs. Zhou *et al.* used the covalent inhibitors H-151 and C-178 as lead compounds to design and synthesize a series of indole-3-ylurea derivatives through bioelectronic isomeric substitution and chemical type hybridization strategies. Among these, the tricyclic compound 4dc exhibited excellent STING inhibitory activity, capable of directly binding to STING and blocking downstream signaling pathways [62]. Furthermore, the acrylamide derivative BPK-25 binds to Cys91 via a bullet-head structure, efficiently inhibiting cGAMP-induced pathway activation in human primary immune cells [63]; nitro-fatty acid derivatives (NO₂-cLA, 9/10-NO₂-OA) [64], on the other hand, modulate multiple sites including Cys88, Cys91, and His16 through covalent modification, demonstrating unique advantages in regulating the tumor immune microenvironment and offering new insights for combination cancer therapy. Chang *et al.* developed a series of nitroalkene STING inhibitors, among which the lead compounds CP-36 and CP-45 [65] block STING palmitoylation by covalently modifying Cys88/91, effectively inhibiting STING-dependent inflammation in vitro and in vivo, and providing new pre-clinical drug candidates for the treatment of STING-related diseases such as SAVI. Based on previously reported 3,4-dihydroisoquinoline-2(1H)-carboxamide inhibitors, Zhou *et al.* [66] designed and synthesized a series of isoindoline-2(1H)-carboxamides STING inhibitors. Among these, compound 3b exhibited nanomolar-level inhibitory activity against both human and mouse STING, with IC₅₀ values of 6.2 nM and 12.5 nM, respectively. It effectively inhibited the STING/TBK1/IRF3 signaling axis and alleviated cisplatin-induced acute kidney injury. Additionally, studies have shown that compound 5c [67] covalently binds to the transmembrane domain of STING, blocking the activation of the STING/TBK1/IRF3 pathway. By restoring mitochondrial function, inhibiting ROS (Reactive Oxygen Species) production, and reducing apoptosis, it exerts potent anti-inflammatory and anti-acute kidney injury effects in Raw. Niu *et al.* used the marine macrocyclic diterpenoid compound Excavatulide B as a scaffold and, through structural optimization, developed the covalent STING inhibitor GHN105 [68]. This compound selectively binds to Cys91 on STING, blocking downstream TBK1/IRF3 signaling. It possesses good oral bioavailability and safety, and has demonstrated significant therapeutic effects in a mouse model of acute colitis.

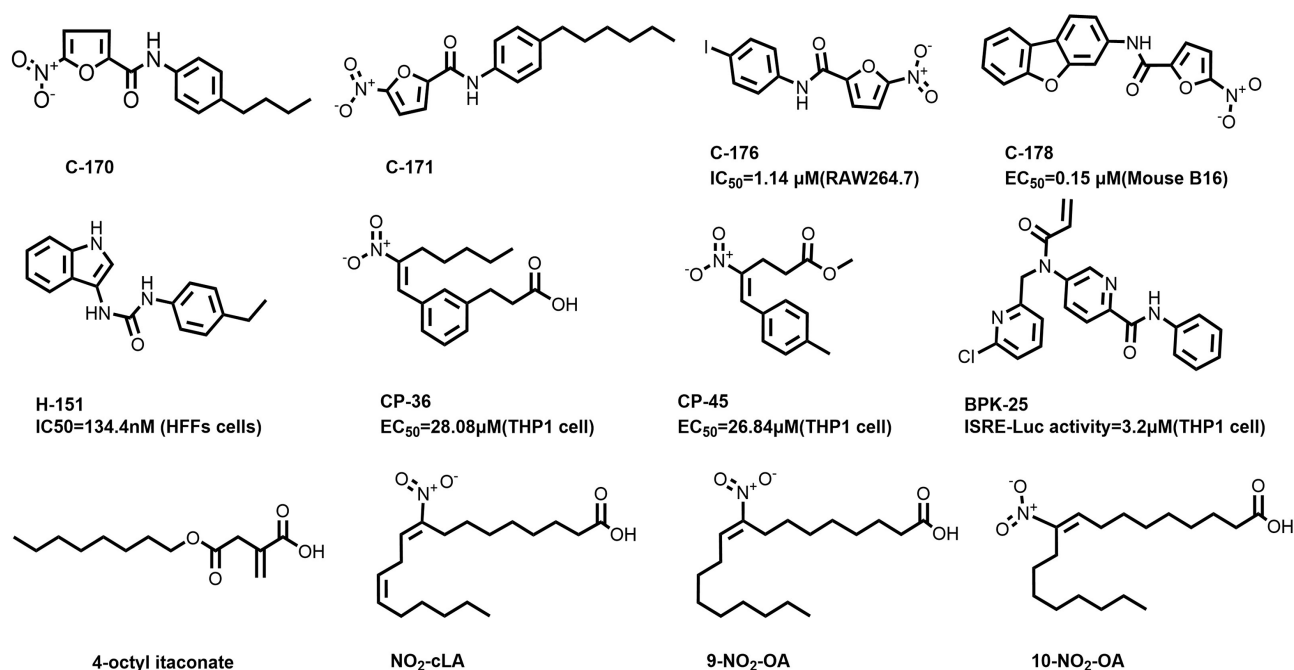


Figure 3. Chemical structures of representative STING inhibitors covalently targeting Cys91. Inhibitory activities (IC₅₀/EC₅₀) in indicated cell lines are annotated below each structure.

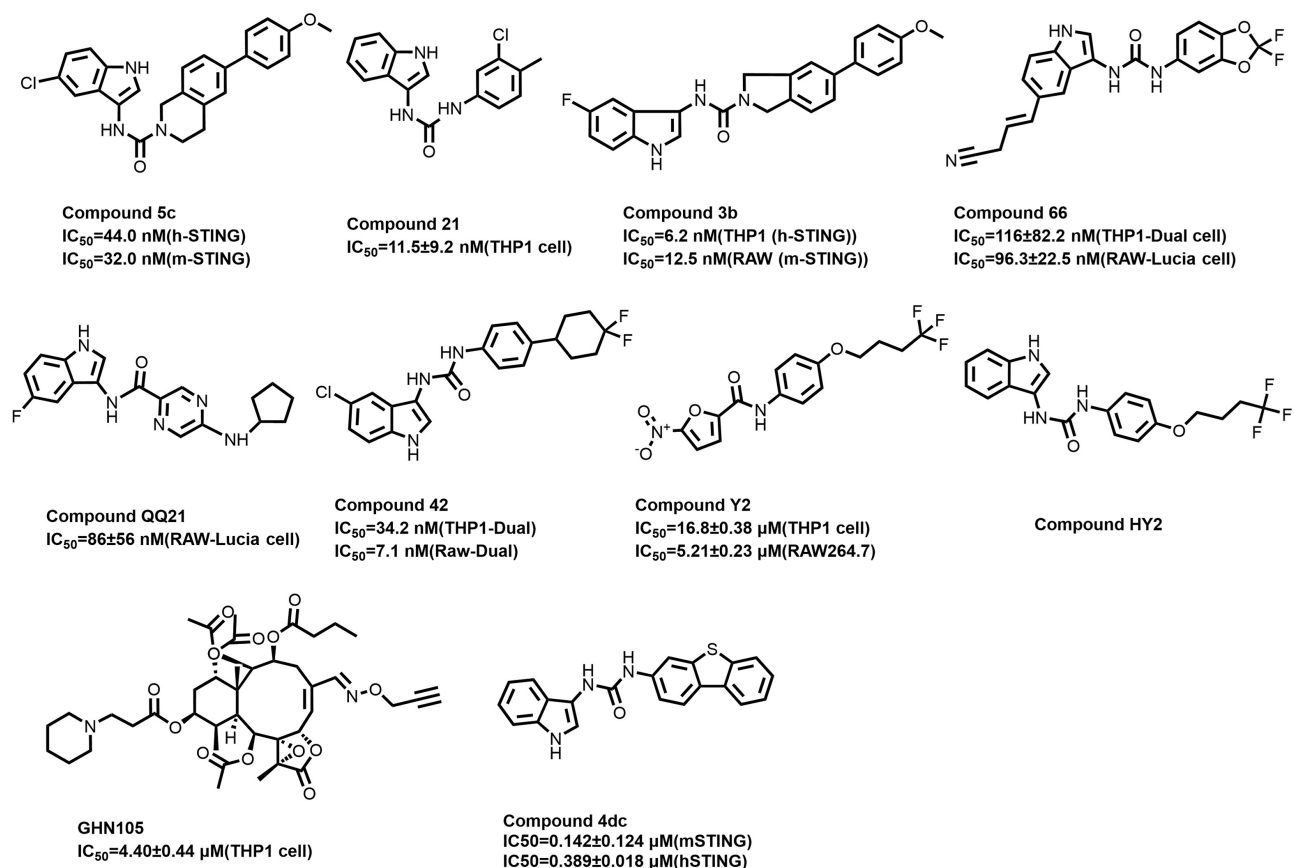


Figure 4. Structural optimization derivatives and novel scaffolds of Cys91-targeting covalent STING inhibitors. IC₅₀/EC₅₀ values in specified cell lines are indicated beneath each structure.

Covalent Cys91-targeted STING inhibitors have emerged as a research hotspot in STING inhibition strategies due to their well-defined mechanism of action, potent *in vivo* activity, and sustained effects. Currently, a diverse library of such inhibitors has been established, encompassing various structural types, from classic H-151 and C-series compounds to novel structurally modified derivatives. Their applications continue to expand, and they show great promise in the treatment and research of various diseases, including autoimmune diseases, neuroinflammation, cancer, and acute kidney injury.

3.2. Competitive CDN Binding Pocket Inhibitors

Competitive CDN pocket inhibitors occupy the LBD of the C-terminal region of STING, competing with endogenous 2'3'-cGAMP and exogenous CDNs for binding. By displacing bound ligand molecules, they lock STING in an open, inactive conformation, thereby blocking downstream signal activation. As a class, these inhibitors are the most clinically advanced, with SN-011 currently in Phase I trials for inflammatory and cancer-associated diseases, and multiple representatives (SN-011, compound 15b, and compounds 11/27) showing cross-species human-mouse activity, though systematic variant-sensitivity profiles remain to be established. These inhibitors exhibit high binding specificity and reversible action, allowing for precise regulation of STING pathway activity according to therapeutic needs. They represent the class of inhibitors currently advancing most rapidly toward clinical translation and have demonstrated significant therapeutic value in the treatment of autoimmune diseases, inflammatory diseases, and cancer-associated inflammation. Competitive CDN binding pocket inhibitors and their inhibitory activities are summarized in **Figure 5**. SN-011 (GUN35901) is the most extensively studied representative compound in this class, exhibiting inhibitory activity in both human and mouse models. SN-011 has now successfully entered Phase I clinical trials, primarily for the treatment of SAVI (self-inflammatory diseases), SLE (systemic lupus erythematosus), and cancer-associated inflammatory diseases. It provides a novel drug candidate for the clinical management of these conditions and accelerates the clinical translation of competitive CDN-binding pocket inhibitors. Compound 18 [69], developed by Merck, specifically binds to the inactive open conformation of STING with an IC_{50} of 68 nM and an oral bioavailability as high as 60%. It efficiently displaces cGAMP and blocks IRF3 recruitment, thereby further inhibiting downstream inflammatory signaling. Natural products such as Astin C, Gelsevirine, and Ginkgetin exert inhibitory effects by competitively occupying the STING ligand-binding pocket. Some of these natural product inhibitors also possess the additional function of promoting STING protein degradation, which further enhances the STING inhibitory effect, overcomes the limitations of a single inhibitory mechanism, and expands the mechanisms of action and application scenarios for this class of inhibitors. Recently, several novel competitive CDN pocket inhibitors have been reported. Compound 15b is a thiazolamide-type STING inhibitor synthesized using SN-011 as a lead

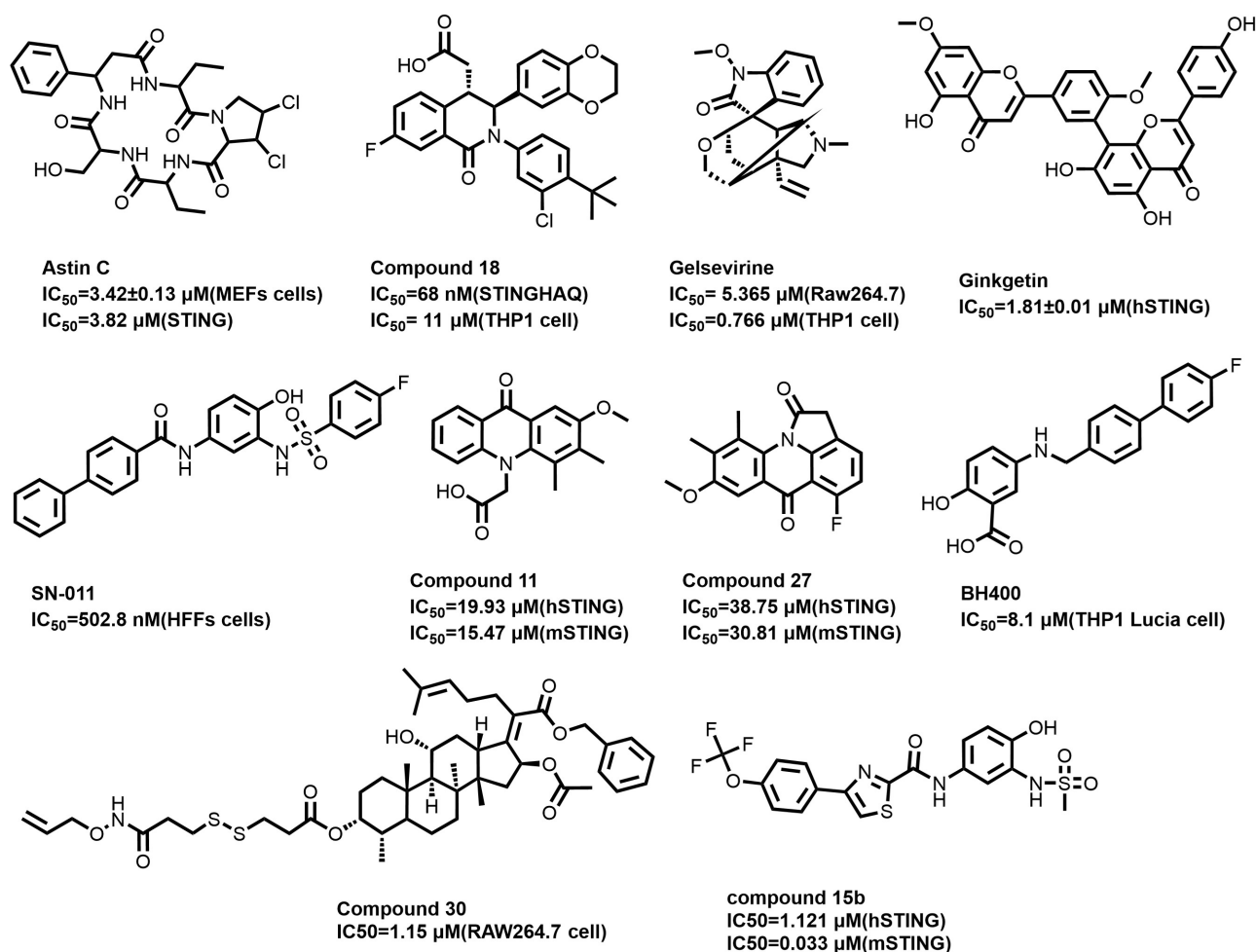


Figure 5. Chemical structures of representative competitive CDN-binding pocket inhibitors. IC_{50} values determined in the indicated cell are annotated below each structure.

compound through a design strategy that disrupts molecular planarity and symmetry [70]. It exhibits potent inhibitory activity against both human and mouse STING, with an IC_{50} value of $0.121\ \mu\text{M}$ for human STING and $0.033\ \mu\text{M}$ for mouse STING; it significantly blocks the phosphorylation of TBK1/IRF3, effectively suppresses the expression of inflammatory factors such as ISG15 (interferon-stimulated genes), and demonstrates excellent *in vivo* anti-inflammatory activity in two mouse inflammatory models, further enhancing the activity and application potential of competitive CDN-binding pocket inhibitors. BH400 exerts its inhibitory effect by directly binding to the CDN-binding pocket of STING [71], while also possessing PPAR α (Peroxisome Proliferator-Activated Receptor Alpha) agonist activity; at the cellular level, its anti-inflammatory and retinal protective effects are significantly superior to those of a single STING inhibitor. Chang *et al.* optimized the structural framework of the mouse STING agonist DMXAA (5,6-dimethylxanthene-4-acetic acid) to synthesize and characterize broad-spectrum STING inhibitors, Compound 11 and Compound 27 [72], both of which exhibit micromolar-level inhibitory activity in human and mouse STING pathways, ef-

fectively blocking 2'3'-cGAMP-induced type I interferon and inflammatory cytokine expression without significant cytotoxicity. Additionally, Compound 30 [73] is the first fusidic acid-derived STING inhibitor, with an IC_{50} of 1.15 μ M, which exerts significant anti-inflammatory and hepatoprotective effects in a mouse sepsis model by directly binding to STING and inhibiting the TBK1/IRF3/NF- κ B signaling axis. It provides a novel molecular scaffold for the development of STING inhibitors derived from natural products and enriches the structural diversity of such inhibitors.

Competitive CDN-binding pocket inhibitors have emerged as a key direction for the clinical translation of STING inhibitors due to their high binding specificity, reversible action, and ease of precise regulation. Currently, a comprehensive research framework for this class of inhibitors has been established, encompassing various structural types such as synthetic compounds and natural products. From the highly active SN-011 and Compound 18 with excellent oral bioavailability to natural product-derived inhibitors and various novel structural derivatives, their inhibitory activity continues to improve.

3.3. Inhibitors That Block STING Oligomerization

Inhibitors that block STING oligomerization act on the protein-protein interaction interfaces of STING homodimers or higher-order oligomers. Notably, this class displays broad human–mouse species coverage and retains inhibitory potency against the common R232 variant, as demonstrated by the UM series; however, all members remain in the preclinical development stage. By preventing dimer formation or further polymerization, they inhibit the interaction between STING and the downstream TBK1, thereby blocking the activation of IRF3 and NF- κ B (NF- κ B-inducing kinase). Their primary advantage is the ability to overcome the resistance of certain mutants to conventional inhibitors. **Figure 6** provides a comprehensive overview of inhibitors that block STING oligomerization, and summarizes their inhibitory potency. BB-Cl-amidine was initially developed as a peptidyl-arginine deaminase (PAD) inhibitor but was later found to covalently bind to Cys148 to block STING oligomerization. It exhibits potent inhibitory activity both in vitro and in vivo, significantly improving inflammation and organ damage in Aicardi-Goutières syndrome (AGS) models. Singh *et al.* developed ASF24 (EC_{50} =0.49 μ M), a triazole-based STING inhibitor with a nitrofurazone moiety [74], which blocks STING oligomerization by covalently modifying Cys292. This compound exhibits excellent metabolic stability, proteome selectivity, and no PAD off-target activity. LB244 [75], developed by Barasa *et al.*, along with its optimized analogs UM-242 (EC_{50} =1.70 μ M) and UM-259 (EC_{50} = 1.50 μ M), block STING oligomerization by covalently modifying Cys292 [76]. These compounds efficiently inhibit the STING signaling pathway in human and mouse models, providing new candidate molecules for the treatment of STING-associated inflammatory diseases. Furthermore, these three compounds maintain potent inhibitory activity against the human R232 variant and primary CD14⁺ mon-

ocytes, demonstrating excellent protein-specific selectivity. UM-203, developed by the same team, is the first reversible covalent STING antagonist [77]. It uses an alkynyl-thiazole as a novel warhead to reversibly bind to Cys292, with an EC_{50} of 1.40 μ M, demonstrating potent inhibition and excellent metabolic stability in both cross-species systems and primary human mononuclear cells; The team's UM-200 [78], on the other hand, employs an acetamide moiety to covalently modify C292/C309 (rather than C91) and block oligomerization, with an EC_{50} (Half Maximal Effective Concentration) of 1.10 μ M. It exhibits dual human-mouse activity and improved metabolic stability. Furthermore, the CDK4/6 (Cyclin-Dependent Kinase 4/6) inhibitor palbociclib can directly bind to the STING Tyr167 site to block its dimerization; its binding affinity is significantly higher than that of endogenous cGAMP, and its anti-inflammatory effects in colitis and autoinflammatory models are comparable to those of H-151.

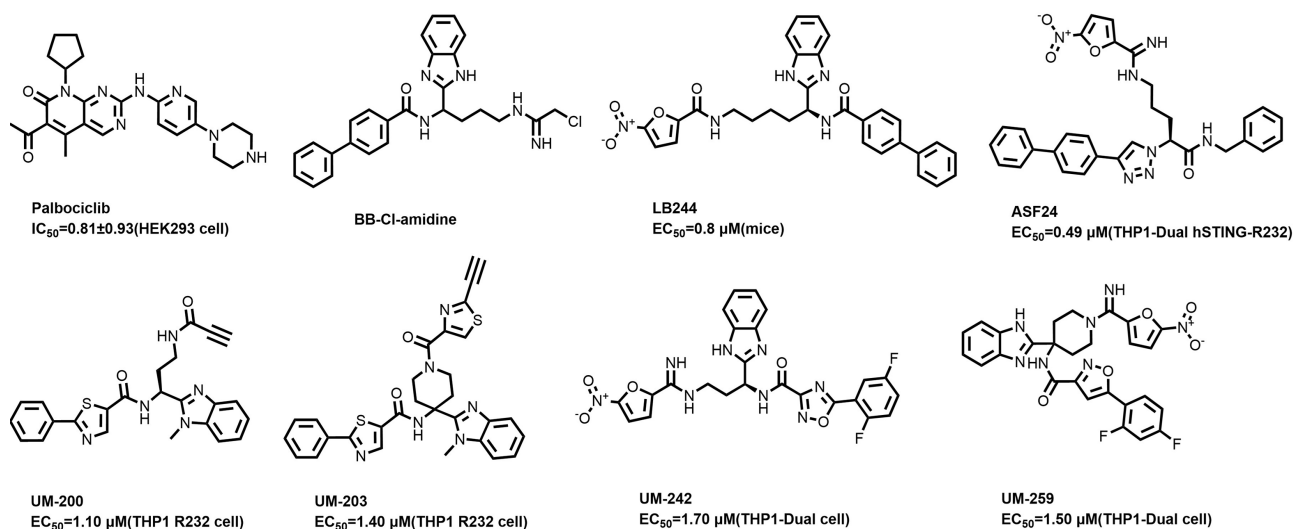


Figure 6. Representative inhibitors blocking STING oligomerization. Chemical structures with inhibitory activities (IC_{50} or EC_{50}) in the indicated cell lines or animal models annotated below each compound.

3.4. STING Inhibitors Targeting Other Mechanisms

In addition to the three classic inhibitor classes mentioned above, numerous compounds inhibit the STING pathway through non-classical mechanisms, including disruption of protein interactions, indirect regulation, and targeted degradation, providing new directions for STING inhibitor development. Overall, inhibitors acting via alternative mechanisms are largely at the preclinical or mechanistic-discovery stage, with 3S-12 demonstrating cross-species cellular activity and the targeted degrader SI-43 exhibiting selective potency against the S154/M155 mutant, underscoring an emerging strategy for variant-specific STING modulation. **Figure 7** provides a systematic overview of STING inhibitors acting through other mechanisms, together with a compilation of their inhibitory potency and associated biological data. The mitochondrial uncoupler CCCP inhibits signal transduction by disrupting the interaction between STING and TBK1 and is primarily used

for mechanistic studies. The hepatic X receptor agonist T0901317 is highly selective, inhibiting only the 2'3'-cGAMP-activated STING pathway, thereby enabling precise endogenous regulation. Omaveloxolone inhibits the STING-NF- κ B signaling axis and shows potential for application in models of bone metastasis. 3S-12, designed by Zhou *et al.* [79], based on an H-151 dimerization strategy, exerts potent inhibition by simultaneously occupying the STING dimer interface, with IC_{50} values of 0.124 μ M and 0.533 μ M in mouse and human cells, respectively. Compound 11h, developed by Han *et al.*, acts by non-covalently binding to the transmembrane domain of STING and significantly alleviates STING-mediated systemic inflammation and cisplatin-induced kidney injury both in vitro and in vivo. Targeted protein degraders can directly degrade the STING protein via the ubiquitin-proteasome system or the lysosomal pathway; their effects are more sustained and can overcome adaptive resistance to inhibitors. As shown in **Table 1**, Representative compounds include SP-23, UNC9036, SD02, ST9, AK59, P8, Degradier-2, and 2 h [80] [81]. Notably, the dual-pocket binding molecule SI-43 [82] achieves potent inhibition and mutant-specific degradation by simultaneously occupying the bottom and side pockets of the STING dimer. This compound selectively degrades the STING S154/M155 mutant via an ubiquitin-proteasome-independent autophagy-lysosomal pathway. Furthermore, Xu He and colleagues developed a smart charge-reversible polymeric degrader called CreTACs [83], which utilizes the acidic microenvironment of rheumatoid arthritis lesions to achieve precise delivery and induces the efficient degradation of the STING protein via the ubiquitin-proteasome pathway, thereby effectively alleviating joint inflammation and bone erosion without causing systemic toxicity.

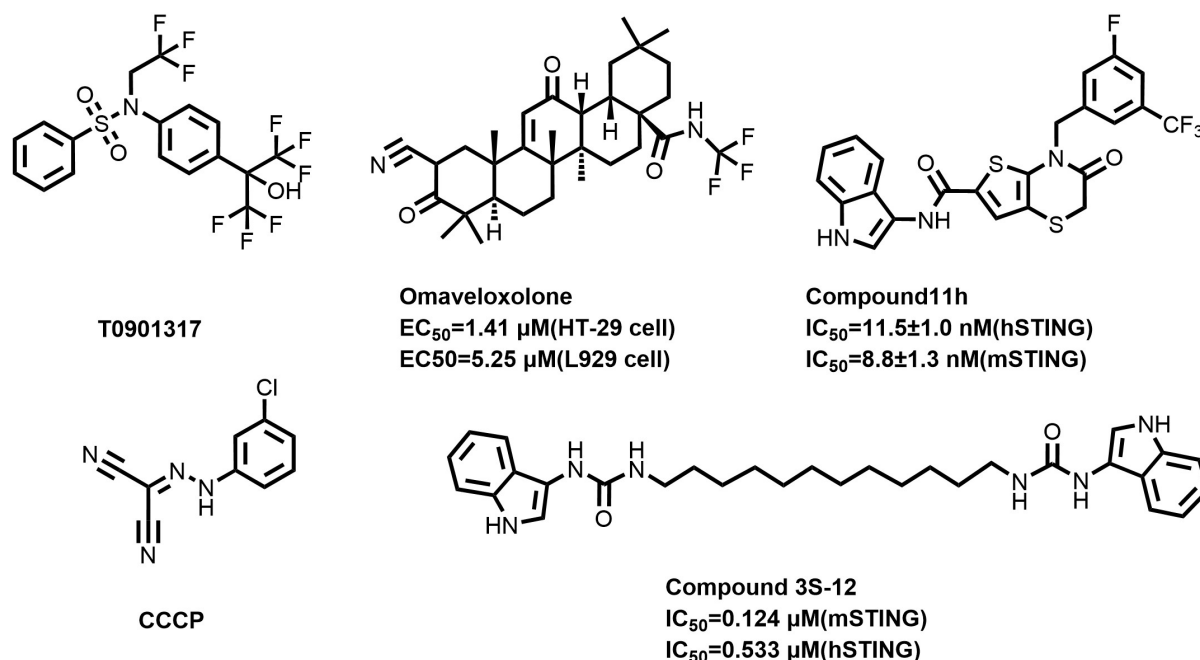


Figure 7. Chemical structures of targeted STING inhibitors acting via alternative mechanisms. Inhibitory activities (IC_{50}/EC_{50}) in the indicated cell lines or against specified STING species are annotated below each structure.

Table 1. Representative STING-targeted protein degraders and their degradation activities.

Compound	Target Protein	DC ₅₀	E3 Ligase	Linker Type
SP23	STING	3.2 μ M	CRBN	Flexible PEG
UNC9036	STING	1.8 μ M	VHL	Rigid alkyl
SD02	STING	0.53 μ M	CRBN	Covalent sulfonyl group
ST9	STING	0.62 μ M	VHL	Rigid aromatic
AK59	STING	-	HERC4	-
P8	STING	-	CRBN	-
Degrader 2	STING	-	-	Dual covalent ligand
2h	STING	3.23 μ M	-	Non-nitro covalent
CreTACs	STING	-	CRBN	PEG-b-P
SI-43	STING (S154/M155)	0.31 μ M (S154)/ 0.76 μ M (M155)	Autophagy-lysosome pathway	Dual-pocket binding design

4. Conclusions and Outlook

As the central adapter protein of the cGAS-STING innate immune pathway, STING's molecular structure, signaling mechanisms, and dual regulatory functions in tumor and inflammatory diseases have been systematically elucidated. Ligand binding, Cys91 palmitoylation, Golgi-translocation, and higher-order oligomerization are key steps in its activation, while genetic polymorphisms and human/mouse species differences are important factors influencing the activity and specificity of small-molecule inhibitors. A central insight emerging from this review is that the therapeutic utility of targeting STING in oncology depends fundamentally on the temporal dynamics of pathway activity: acute, moderate STING activation is therapeutically desirable in immunologically cold tumors, whereas chronic STING hyperactivation or complete pathway inactivation promotes immune suppression and tumor progression, making STING inhibition the preferred strategy under these conditions. Currently, STING inhibitors have emerged in four major research directions: covalent targeting of Cys91, competitive binding to the CDN ligand pocket, blocking the oligomerization interface, and targeting protein degradation. Significant progress has been made in molecular mechanisms, compound scaffolds, and modes of action; however, fundamental scientific challenges remain, including strong species specificity, poor inhibitory effects against clinically prevalent mutants, insufficient molecular selectivity, and incomplete elucidation of the mechanism of action.

Future efforts should advance basic research in depth across multiple levels. At the molecular structural level, we will rely on high-resolution structural data to precisely elucidate the binding patterns and conformational changes of inhibitors, establish structure-activity relationships for different variants of human STING,

and conduct structural optimization of highly specific and potent inhibitors using techniques such as molecular docking and virtual screening; At the mechanism-of-action level, we will systematically elucidate the functions of non-canonical STING signaling pathways and cross-regulatory networks, identify novel inhibition sites and regulatory mechanisms, and refine the dynamic regulation and feedback mechanisms of the pathway; At the molecular design level, we will expand chemical scaffolds through rational design and high-throughput screening, focusing on breakthroughs in highly selective inhibitors and STING degraders that exhibit dual human-mouse activity and target high-frequency mutants, thereby overcoming issues such as species differences, mutation-induced resistance, and signal rebound; At the functional regulation level, we will establish quantitative correlations between STING activation intensity, duration, and cellular phenotypes, and clarify the regulatory boundaries of the pathway's dual effects; At the model and methodology level, we will construct basic research models that more closely reflect the characteristics of human STING, develop a multidimensional evaluation system, and provide robust theoretical and technical support for the mechanism studies and optimized design of STING-targeting molecules. Ultimately, we will comprehensively elucidate the fundamental biological principles of the STING pathway and lay a complete theoretical foundation for subsequent precision-targeted interventions.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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