Supplemental Report

Identification and Structural Analysis of VENT-03, a Clinical-Stage cGAS Inhibitor

1. Introduction

1.1. Objective

This report details the analysis undertaken to identify the specific chemical structure of VENT-03, the lead clinical development candidate targeting cyclic GMP-AMP synthase (cGAS) developed by Ventus Therapeutics. The analysis integrates information from patent literature, scientific publications, and public disclosures made by the company.

1.2. Background on cGAS and VENT-03

Cyclic GMP-AMP synthase (cGAS) is a critical enzyme in the innate immune system, acting as a primary sensor for cytosolic double-stranded DNA (dsDNA).[1] DNA should normally reside within the nucleus or mitochondria; its presence in the cytoplasm signals danger, often resulting from pathogen invasion (viral or bacterial DNA) or cellular damage leading to the leakage of mitochondrial or nuclear DNA.[1] cGAS acts as an intracellular pattern recognition receptor, binding to this misplaced dsDNA.[6] Upon binding dsDNA, cGAS undergoes a conformational change and catalyzes the synthesis of the cyclic dinucleotide second messenger 2'3'-cyclic GMP-AMP (2'3'-cGAMP) from ATP and GTP.[3] 2'3'-cGAMP subsequently binds to and activates the Stimulator of Interferon Genes (STING) protein, an adaptor protein located on the endoplasmic reticulum.[1] STING activation initiates downstream signaling cascades involving kinases like TBK1, leading to the phosphorylation and activation of transcription factors, primarily IRF3 and NF-κB.[1] These transcription factors translocate to the nucleus and drive the expression of Type I interferons (IFNs) and other pro-inflammatory cytokines and chemokines.[1]

While this pathway is essential for host defense against infections, aberrant activation of the cGAS-STING pathway by self-DNA is strongly implicated in the pathogenesis of numerous autoimmune and inflammatory diseases.[1] In these conditions, the immune system mistakenly recognizes the body's own DNA as foreign, leading to chronic inflammation and tissue damage driven by excessive Type I IFN production (an "interferonopathy").[2] Diseases linked to pathogenic cGAS activation include Systemic Lupus Erythematosus (SLE), where loss of tolerance to nuclear antigens like dsDNA is a hallmark [9], Aicardi-Goutières Syndrome (AGS), dermatomyositis (DM), systemic sclerosis, Sjögren's disease, and potentially neurodegenerative conditions.[1] For instance, studies have shown heightened cGAS-STING pathway activation in the skin of SLE and cutaneous lupus erythematosus (CLE) patients, which can be exacerbated by triggers like UVB exposure leading to photosensitivity.[4] Consequently, inhibiting cGAS activity represents a highly promising therapeutic strategy to dampen the pathological inflammation in

these conditions.[1] Despite significant efforts within the pharmaceutical industry, developing potent, selective, and orally bioavailable small-molecule cGAS inhibitors has proven exceptionally challenging due to the nature of the enzyme and its binding sites, with no candidates reaching the market to date.[5]

Ventus Therapeutics, a clinical-stage biopharmaceutical company founded in 2019 [14], utilized its proprietary ReSOLVE™ platform to tackle challenging drug targets like cGAS.[2] In January 2023, Ventus announced the nomination of VENT-03 as its potential first-in-class cGAS inhibitor development candidate.[5] VENT-03 subsequently entered Phase 1 clinical trials in late 2023/early 2024 [15] and successfully completed these trials in October 2024.[9] Ventus plans to advance VENT-03 into Phase 2 trials for SLE starting in 2025.[6] Public descriptions characterize VENT-03 as a potent, selective, oral, first-in-class cGAS inhibitor with excellent drug-like properties and a favorable pharmacokinetic profile supporting once-daily dosing.[2]

2. Methodology

The identification of VENT-03's structure was pursued through a multi-faceted analytical approach:

1. **Discovery Platform Context:** Understanding the capabilities of Ventus's ReSOLVE™ platform was key. This platform integrates cutting-edge structural biology (including solving high-resolution co-crystal structures), biophysics, advanced computational chemistry, physics-based simulations (like unrestrained molecular dynamics), and artificial intelligence/machine learning (AI/ML).[3] ReSOLVE™ is designed to model the full spectrum of protein dynamics, analyze and visualize protein targets to identify previously unknown or transiently accessible binding pockets, and create dynamic "hydrocophore" blueprints guiding virtual screening of billions of compounds to rapidly generate novel chemical matter with optimal binding affinity.[5] This platform reportedly provided unique insights into the cGAS binding pocket, enabling the design of VENT-03.[3]
2. **Patent Landscape Analysis:** Systematic identification and analysis of patents assigned to Ventus Therapeutics U.S., Inc. related to cGAS inhibitors. Priority was given to patents with filing and priority dates aligning with the known development timeline of VENT-03. Key data extracted included core chemical scaffolds, specific exemplified compounds (structures where available, biological activity such as cGAS IC50 values), claimed chemical space, and preferred embodiments.
3. **Scientific Literature Review:** Examination of peer-reviewed publications and conference abstracts authored by Ventus Therapeutics personnel or collaborators concerning cGAS inhibitors. This involved searching for disclosed chemical structures, associated biological data, and any explicit or implicit links to VENT-03.
4. **Public Disclosure Correlation:** Analysis of press releases, company website information,

investor presentations (including the May 25, 2023 event), and scientific meeting abstracts related to VENT-03. Key descriptive information regarding potency, mechanism, development status, structural class hints, and timeline was extracted. Biological assays mentioned in disclosures, such as biochemical inhibition assays and cellular assays (e.g., measuring downstream effects like cGAMP production or IFN/cytokine signaling in relevant cell types like THP-1 monocytes or whole blood assays), were noted to correlate potency data.[4]

5. **Data Synthesis and Correlation:** Cross-referencing structural information and biological data (particularly potency measured in relevant assays) from patents and publications with the descriptive characteristics of VENT-03 obtained from public disclosures. The analysis focused on identifying convergence points where specific chemical entities from relevant Ventus patents matched the timeline, potency profile, and qualitative descriptions of VENT-03.
6. **Hypothesis Generation and Refinement:** Formulation of a primary hypothesis regarding the chemical structure of VENT-03 based on the strongest convergence of evidence, followed by an assessment of confidence and consideration of alternative possibilities.

3. Timeline and Contextual Analysis

Establishing a timeline is crucial for correlating patent filings with the development candidate selection:

- **2019:** Ventus Therapeutics founded.[14]
- **Feb 5, 2019:** Priority date for WO2019153002A1 (Tetrahydro-pyrido[4,3-b]indole inhibitors, likely prior art/early work).[1]
- **2020:** Ventus screens its first target using the ReSOLVE™ platform.[9]
- **Mar 21, 2022:** Priority date for WO2023183275A1 (Ventus - Hexahydropyrido[4,3-b]indolyl ketone derivatives).[23]
- **Dec 20, 2022:** Priority date for WO2024137752A1 (Ventus - Azepino[4,5-b]indolone inhibitors).[5]
- **Jan 4, 2023:** Ventus nominates VENT-03 as a potential first-in-class cGAS inhibitor development candidate.[5]
- **Apr 17, 2023:** Ventus presents data on VENT-03 potency and PK profile at Keystone Symposium.[21]
- **May 25, 2023:** Ventus hosts Program Spotlight event focused on VENT-03.[25]
- **Sep 28, 2023:** Publication date for WO2023183275A1.[24]
- **Jan 3, 2024:** Ventus announces first participant dosed in Phase 1 trial for VENT-03.[15]
- **Jun 27, 2024:** Publication date for WO2024137752A1.[5]
- **Oct 31, 2024:** Ventus announces successful completion of Phase 1 trial for VENT-03.[9]
- **Nov 17, 2024:** Ventus presents ACR abstract on VENT-03 discovery and preclinical data.[8]

- **Mar 25, 2025:** Ventus announces publication in Communications Chemistry regarding structure-based optimization of a *different* series of cGAS inhibitors.[6]
- **2025 (Planned):** Initiation of Phase 2 trial for VENT-03 in SLE.[6]

This timeline highlights the critical window between late 2022 and early 2023 for the selection and patent protection of VENT-03. Patent applications with priority dates falling within or immediately preceding this period are of highest relevance.

4. Patent Landscape Analysis

4.1. Ventus Therapeutics Patent Portfolio

Searches identified multiple patent families assigned to Ventus Therapeutics U.S., Inc..[23] While several relate to NLRP3 inhibitors (e.g., VENT-01, VENT-02) [14], key applications targeting cGAS inhibitors were identified and analyzed.

4.2. Analysis of WO2024137752A1 (Azepino[4,5-b]indolones) - The Key Patent

- **Identifier:** WO2024137752A1
- **Assignee:** Ventus Therapeutics U.S., Inc. [5]
- **Dates:** Priority Date: December 20, 2022; Filing Date: December 20, 2023; Publication Date: June 27, 2024.[5]
- **Core Scaffold:** The patent discloses novel azepino[4,5-b]indolone derivatives as cGAS inhibitors.[5] The general structure claimed is represented by Formula IIa: Formula IIa *(Structure depiction based on description in [5], specific image not available in snippets)* Wherein X, R^1, R^3, R^4, R^6, R^7, R^8, R^9 represent various substituents defined in the patent.[5]
- **Explicit Link to VENT-03:** Crucially, the background section of this patent explicitly mentions Ventus Therapeutics' announcement of VENT-03 in January 2023 as a cGAS inhibitor development candidate.[5] This provides a direct contextual link between this specific chemical series and the clinical candidate.
- **Exemplified Compounds and Potency:** The patent exemplifies numerous compounds within this class and provides biological data (Table 2A and 2B).[5] A significant number of examples exhibit exceptionally high potency, with cGAS IC50 values reported as '< 0.001 µM' (i.e., sub-nanomolar) in both biochemical assays and cell-based assays (measuring downstream effects like cGAMP production or IFN/cytokine signaling).[5] Examples demonstrating this high potency include Examples 32, 33, 36, 38, 39, 40 (Isomer 1), 41 (Isomer 2), 42 (Isomer 1), 43 (Isomer 2), 44-49, 50 (Isomer 1), 51 (Isomer 1), 52, 53 (Isomer 1), 54 (Isomer 2), 55 (Isomer 1), 56 (Isomer 2), 57, 58 (Isomer 1), 59 (Isomer 2), 60-61, and many others up to Example 177.[5]
- **Preferred Embodiments:** The patent details numerous preferred embodiments, specifying preferred substituents at various positions (e.g., X and R^4 as halo, particularly chloro; R^7 as

methyl; specific functional groups for R³).[5] Specific compounds are listed as preferred in Embodiments 57, 58, and 59.[5]

- **Significance:** The combination of (1) the priority date (Dec 20, 2022) immediately preceding the VENT-03 nomination (Jan 2023), (2) the explicit mention of VENT-03 in the patent text, and (3) the disclosure of novel structures with sub-nanomolar potency consistent with descriptions of VENT-03 ("excellent potency," "full target inhibition" [9]) makes this patent the most critical piece of evidence for identifying the VENT-03 structure. The azepino[4,5-b]indolone scaffold represents a novel chemical class for cGAS inhibition, aligning with the "first-in-class" designation of VENT-03.[2]

4.3. Analysis of WO2023183275A1 (Hexahydropyrido[4,3-b]indolyl ketones) - Earlier Series

- **Identifier:** WO2023183275A1
- **Assignee:** Ventus Therapeutics U.S., Inc. [24]
- **Dates:** Priority Date: March 21, 2022; Publication Date: September 28, 2023.[23]
- **Core Scaffold:** Discloses hexahydropyrido[4,3-b]indolyl ketone derivatives as cGAS modulators.[23] This scaffold is distinct from the azepino[4,5-b]indolones in WO2024137752A1.
- **Link to VENT-03:** No explicit mention of VENT-03 was found in the available snippets for this patent application.
- **Data Limitations:** Available snippets provide limited structural or potency data.[30]
- **Significance:** The earlier priority date (March 2022) compared to WO2024137752A1 (December 2022) suggests this chemical series likely represents an earlier stage of Ventus's cGAS inhibitor program. Given that the later patent (WO2024137752A1) explicitly mentions VENT-03 and aligns perfectly with the nomination timeline, it is highly probable that the azepino[4,5-b]indolone series, not the hexahydropyrido[4,3-b]indolyl ketone series, encompasses the clinical candidate VENT-03. This earlier series may have been explored as a precursor or alternative chemotype that was ultimately not selected for clinical development.

4.4. Analysis of WO2019153002A1 - Prior Art/Early Work

- **Identifier:** WO2019153002A1
- **Assignee:** Not Ventus Therapeutics (Assignee appears related to academic/other institutions based on context in later patents, though specific assignee not clear from snippets).
- **Dates:** Priority Date: February 5, 2018.[1]
- **Core Scaffold:** Discloses 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole derivatives, specifically 1-(3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-2-hydroxyethanones, as cGAS inhibitors.[1]
- **Significance:** This patent application, with a priority date significantly earlier than Ventus's

likely selection period for VENT-03, represents prior art or very early work in the field. It is explicitly mentioned in the background section of Ventus's WO2024137752A1 patent [5], indicating it describes a known, distinct chemical series from which Ventus sought to differentiate. The compounds described likely do not represent VENT-03.

5. Scientific Publication Analysis

5.1. Communications Chemistry (March 2025)

- **Source:** Ventus Therapeutics authors.[6]
- **Content:** This paper details structure-based optimization efforts for cGAS inhibitors, focusing on understanding binding modes and species-specific potency differences (related to Thr/Ile residues in human vs. mouse cGAS).[6] It discloses specific structures, including Compound **2** ((S)-1-(6,7-dichloro-1-methyl-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indol-2-yl)-2-methoxyethan-1-one), which belongs to the pyrido[4,3-b]indole class (related to WO2019153002A1).[31]
- **Potency Data:** Compound **2** showed an IC50 of approximately 3 µM in a THP1 cell-based assay.[31] While other compounds like G150 showed nanomolar biochemical potency, significant species differences were noted.[31]
- **Relevance to VENT-03:** The publication explicitly states that the described studies "will inform our strategies to develop the next generation of potent cGAS inhibitors beyond VENT-03".[6] This clearly indicates that the chemical matter described (pyrido[4,3-b]indoles) and their associated potencies (µM cellular IC50 for Compound **2**) are distinct from the clinical candidate VENT-03. VENT-03, described as having "excellent potency" and achieving "full target inhibition" in Phase 1 [9], would be expected to possess significantly higher cellular potency, likely in the low nanomolar or sub-nanomolar range demonstrated by the azepino[4,5-b]indolones in WO2024137752A1.[5] This publication likely describes earlier or parallel research efforts by Ventus, possibly related to the scaffolds in WO2019153002A1 or WO2023183275A1.

5.2. ACR Convergence Abstract (November 2024)

- **Source:** Ventus Therapeutics authors.[8]
- **Content:** This abstract describes the discovery process for VENT-03, involving high-throughput screening (HTS), structure-activity relationship (SAR) studies, and the proprietary ReSOLVE™ platform.[8] VENT-03 is described as a novel, selective cGAS inhibitor with "excellent drug-like properties" and robust pharmacodynamic activity in preclinical models.[4]
- **Preclinical Validation:** The abstract reports that "tool molecules of the VENT-03 chemotype" demonstrated significant efficacy in the *Trex1^-/-^* mouse model, which recapitulates hallmarks of SLE including elevated Type I IFN activity.[4] Therapeutic dosing

led to a down-modulation of IFN activity and reduced expression of NF-κB driven pro-inflammatory mediators.[4] Furthermore, markers of cytotoxic CD8 T-cell activity were reduced, suggesting an impact on adaptive immunity in complex inflammation.[4] In a model of photosensitivity using UVB-exposed *Trex1^-/-* mice, cGAS inhibition reduced markers of dermal inflammation and improved skin integrity.[4] These findings align with observations of heightened cGAS-STING pathway activation in SLE and CLE patients.[4]

- **Structure Disclosure:** Crucially, the abstract does *not* disclose the specific chemical structure or class of VENT-03 or its chemotype.[8]
- **Significance:** This abstract serves as public confirmation of VENT-03's preclinical validation in relevant disease models around the time of Phase 1 completion. The reference to a specific "VENT-03 chemotype" implies the existence of a defined structural class developed by Ventus, consistent with the focused nature of the WO2024137752A1 patent application. The lack of structural disclosure is standard for conference abstracts preceding full publication or patent disclosure.

6. Synthesis and Structure Hypothesis for VENT-03

6.1. Convergence of Evidence

The identification of VENT-03's structural class relies on the strong convergence of multiple lines of evidence, primarily anchored by the patent application WO2024137752A1:

1. **Direct Link and Timing:** WO2024137752A1, assigned to Ventus Therapeutics, has a priority date of December 20, 2022, immediately preceding the public nomination of VENT-03 in January 2023.[5] Furthermore, the patent text explicitly references the VENT-03 development candidate announcement.[5] This temporal proximity and direct mention create an exceptionally strong link between the patent's content and the clinical candidate.
2. **Novel Scaffold:** The patent discloses a novel class of azepino[4,5-b]indolone cGAS inhibitors.[5] This novelty aligns perfectly with the description of VENT-03 as a "first-in-class" molecule.[2]
3. **Potency Match:** Numerous examples within WO2024137752A1 demonstrate exceptionally high potency, with biochemical and cellular IC50 values below 1 nM.[5] This aligns precisely with public descriptions of VENT-03 possessing "excellent potency" [15] and achieving "full target inhibition" in Phase 1 studies.[9] Such high potency is expected for a clinical candidate intended for once-daily oral dosing.[9]
4. **Exclusion of Alternatives:** Other Ventus patent applications (WO2023183275A1) describe different scaffolds (hexahydropyrido[4,3-b]indolyl ketones) and have earlier priority dates without an explicit link to VENT-03 found in snippets, making them less likely candidates.[23] Scientific publications from Ventus describe different chemical matter (pyrido[4,3-

b]indoles) with lower potency, explicitly stating the work informs efforts "beyond VENT-03".[6] Prior art patents describe distinct scaffolds.[1]

6.2. Proposed Structural Class and Characteristics

Based on the compelling convergence of evidence, the primary hypothesis is that **VENT-03 belongs to the azepino[4,5-b]indolone class of cGAS inhibitors disclosed in patent application WO2024137752A1**.

Specifically, VENT-03 is highly likely to be one of the exemplified compounds within this patent that exhibits **sub-nanomolar (**IC50<0.001 **μM) inhibitory activity in both biochemical and relevant cellular assays** (e.g., measuring downstream IFN/cytokine signaling).[5] These compounds generally conform to the core structure represented by Formula IIa.[5]

While the exact example corresponding to VENT-03 cannot be definitively determined from the provided information alone (as final selection depends on comprehensive preclinical profiling including pharmacokinetics, safety, and manufacturability), the structure will possess the core azepino[4,5-b]indolone framework with specific substitutions leading to the observed high potency and favorable drug-like properties mentioned in disclosures.[8] Candidates likely feature preferred substitutions highlighted in the patent's embodiments section.[5]

6.3. Detailed Justification

The conclusion that VENT-03 is an azepino[4,5-b]indolone from WO2024137752A1 is strongly supported. The patent's priority date aligns perfectly with the candidate nomination timeline. The explicit mention of VENT-03 within this patent application [5] serves as a direct bridge between the disclosed chemical series and the development candidate. The novelty of the azepino[4,5-b]indolone scaffold [5] matches the "first-in-class" description of VENT-03.[2] Most importantly, the exceptionally high, sub-nanomolar potency demonstrated by numerous examples in this patent [5] is consistent with the requirements for a clinical candidate and matches the qualitative descriptions of VENT-03's "excellent potency" and ability to achieve "full target inhibition" at tolerated doses in Phase 1.[9] In contrast, other potential chemical series linked to Ventus or the cGAS target either predate the relevant timeframe (WO2019153002A1 [1]), likely represent earlier/alternative programs (WO2023183275A1 [24]), or describe different scaffolds with lower potency that are explicitly stated as not being VENT-03 (Comm Chem paper [6]). The collective weight of evidence points unequivocally to the azepino[4,5-b]indolone series from WO2024137752A1.

6.4. Clinical Profile Confirmation (Phase 1 Results)

The successful completion of the Phase 1 trial further supports the viability of the selected candidate, VENT-03. The trial, involving 72 healthy volunteers, demonstrated that VENT-03 was

safe and well-tolerated across a broad range of single and multiple ascending doses, including doses exceeding those planned for Phase 2.[8] No dose-limiting toxicities or serious adverse events were reported, and any treatment-related adverse events were mild and transient.[8] Crucially, VENT-03 exhibited a favorable pharmacokinetic (PK) profile suitable for once-daily oral dosing.[8] Pharmacodynamic (PD) measures confirmed that VENT-03 reached plasma concentrations sufficient for full target inhibition.[8] These positive Phase 1 results provide clinical validation for the drug-like properties and potency suggested by the preclinical data and patent disclosures.[8]

7. Confidence Assessment and Alternative Considerations

7.1. Confidence Level

High.

The confidence level in identifying the **structural class** of VENT-03 as an azepino[4,5-b]indolone derivative disclosed in WO2024137752A1 is high. This assessment is based on the strength, consistency, and directness of the converging evidence:

- **Strength:** The explicit mention of VENT-03 in the relevant patent application [5] and the disclosure of numerous sub-nanomolar inhibitors [5] are strong pieces of evidence. The positive Phase 1 data confirms the clinical viability of the candidate.[8]
- **Consistency:** The timeline of the patent filing aligns perfectly with the candidate nomination.[5] The described potency in the patent matches the qualitative descriptions of VENT-03 from multiple company communications and the confirmed target engagement in Phase 1.[5] The novel scaffold aligns with the "first-in-class" designation.[5]
- **Directness:** The link between the patent series and the candidate name is explicitly made within the patent document itself.[5]

7.2. Remaining Ambiguities and Strategies for Definitive Identification

- **Specific Example Uncertainty:** The primary remaining ambiguity is the identification of the *exact* exemplified compound within WO2024137752A1 that corresponds to VENT-03. Patent applications typically include multiple highly potent examples surrounding the lead candidate to ensure broad protection. While examples listed as preferred embodiments [5] or those with the most consistently high potency across assays [5] are the most probable candidates, pinpointing the single structure requires definitive confirmation.
- **Strategies for Definitive Identification:** Resolving this final ambiguity typically relies on future disclosures or more granular analysis:
  - **Monitoring Future Disclosures:** Companies often reveal the specific structure of clinical candidates as development progresses. Key sources to monitor include:
    - *Scientific Publications:* Peer-reviewed papers detailing the discovery, full

preclinical characterization, or clinical results of VENT-03.
    - *Conference Presentations:* Full data presentations from the Phase 1 trial (which Ventus plans to present [16]) or presentations at major scientific meetings (e.g., future ACR, EULAR, Keystone Symposia) detailing Phase 2 results or further preclinical work.[3]
    - *Updated Patent Filings:* Subsequent patent applications or granted patents related to VENT-03 might provide more specific structural details or narrow the focus.
  - **Deeper Patent Analysis (WO2024137752A1):** A more granular re-examination of the key patent application [5] could yield further clues:
    - *Preferred Embodiments:* Close scrutiny of compounds explicitly listed as "preferred" or "particularly preferred" in the text or claims, as these often represent or are structurally very close to the lead candidate.[5]
    - *Data Completeness:* Identifying examples with the most comprehensive dataset (e.g., tested across multiple biochemical and cellular assays, potentially including *in vivo* PK or efficacy data if disclosed within the patent).
    - *Synthetic Route Analysis:* Examining the described synthetic methods for indications of a particularly optimized or highlighted route leading to a specific compound.
  - **Cross-Referencing Databases:** Searching specialized chemical databases (e.g., PubChem, ChemSpider, SciFinder, Reaxys) using the azepino[4,5-b]indolone scaffold combined with assignee (Ventus Therapeutics) or keywords (cGAS inhibitor, VENT-03) might uncover public disclosures, although this is less common for compounds in early clinical development.
  - **Clinical Trial Information:** Monitoring official clinical trial registry entries (e.g., ClinicalTrials.gov) for VENT-03.[5] While the structure itself is not listed, associated publications or presentation references linked to the trial identifier may appear over time as results are disseminated.
- **Discounted Alternatives:**
  - *Hexahydropyrido[4,3-b]indolyl ketones (WO2023183275A1):* Considered a plausible alternative initially due to Ventus assignment, but discounted due to its earlier priority date (March 2022), the lack of an explicit link to VENT-03 in available information, and the emergence of the later WO2024137752A1 patent which *does* explicitly mention VENT-03 and aligns perfectly with the nomination timeline.[5] This series likely represents an earlier or parallel discovery effort.
  - *Pyrido[4,3-b]indole Derivatives (Comm Chem Paper):* Explicitly ruled out as VENT-03 based on the authors' statement that the work informs strategies "beyond VENT-03" [6] and the comparatively lower cellular potency reported for key examples like Compound **2**.[31]

- *Tetrahydro-pyrido[4,3-b]indole Derivatives (WO2019153002A1):* Discounted as prior art/early work based on the much earlier priority date and its citation as background in Ventus's key patent.[1]

8. Conclusion

Based on a rigorous analysis of patent literature, scientific publications, and public disclosures, this report concludes with high confidence that VENT-03, Ventus Therapeutics' first-in-class clinical-stage cGAS inhibitor, belongs to the **azepino[4,5-b]indolone** chemical class.

The primary evidence supporting this conclusion is derived from patent application **WO2024137752A1**, assigned to Ventus Therapeutics. This application carries a priority date of December 20, 2022, aligning perfectly with the nomination of VENT-03 in January 2023. Crucially, the text of this patent explicitly mentions the VENT-03 development candidate. Furthermore, WO2024137752A1 discloses numerous examples of novel azepino[4,5-b]indolone derivatives exhibiting exceptionally high potency, with biochemical and cellular cGAS IC50 values below 1 nM. This potency profile is consistent with the public descriptions of VENT-03 as having "excellent potency" and achieving "full target inhibition" in clinical studies, further validated by the successful Phase 1 trial results demonstrating safety, appropriate pharmacokinetics for once-daily dosing, and robust pharmacodynamics.

While the specific exemplified compound corresponding to VENT-03 cannot be identified with absolute certainty without further disclosure, it is highly probable that VENT-03 is one of the sub-nanomolar azepino[4,5-b]indolone examples detailed within WO2024137752A1. Definitive identification will likely require future public disclosures by Ventus Therapeutics through scientific publications or conference presentations, or potentially through more granular analysis of patent filings or database entries as outlined above. Alternative chemical series described in earlier patents or publications have been discounted based on timeline inconsistencies, lower potency, or explicit statements differentiating them from the clinical candidate.

The identification of the azepino[4,5-b]indolone scaffold as the structural basis for VENT-03 represents a significant step in understanding this novel therapeutic agent targeting the cGAS-STING pathway for the treatment of autoimmune and inflammatory diseases like SLE.

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