# Patent Landscape Review: Small Molecule cGAS Inhibitors

## 1. Executive Summary

This report provides a comprehensive patent landscape analysis of small molecule inhibitors targeting cyclic GMP-AMP synthase (cGAS), focusing on the period from 2015 to the present, with geographic coverage including the US, EP, WO, CN, and JP jurisdictions. The analysis concentrates on published applications and granted patents relevant to autoimmune and inflammatory diseases.

The cGAS-STING pathway is a critical component of the innate immune system, detecting cytosolic DNA and triggering inflammatory responses, primarily through type I interferon (IFN-I) production.[1] While essential for host defense against pathogens, aberrant activation of this pathway by self-DNA is strongly implicated in the pathogenesis of numerous autoimmune and inflammatory conditions, including Systemic Lupus Erythematosus (SLE), Aicardi-Goutières Syndrome (AGS), and Rheumatoid Arthritis (RA).[4] Consequently, inhibiting cGAS activity with small molecules has emerged as a highly attractive therapeutic strategy.[7]

Patenting activity for small molecule cGAS inhibitors has surged since 2015, coinciding with a deeper understanding of the pathway's role in disease and the availability of structural information enabling drug design.[9] Filing trends show sustained high activity, indicating intense and ongoing research and development. Patent filings are globally distributed, with the US, EP, and WO jurisdictions representing the major focus, although significant activity is also observed in CN and JP, reflecting the global interest and market potential.[13]

The competitive landscape features a mix of large pharmaceutical companies (e.g., Novartis, Merck, Roche), specialized biotechnology firms (e.g., ImmuneSensor Therapeutics, Ventus Therapeutics, IFM Therapeutics/IFM Due, BellBrook Labs), and academic institutions (notably the University of Texas System, linked to foundational discoveries and subsequent licensing).[11] This diverse set of players employs varied strategies, with large pharma often exploring broader chemical space and biotechs frequently focusing on specific

scaffolds or platform technologies, sometimes leading to faster clinical translation. Collaborations and acquisitions, such as Novartis' acquisition of IFM Due, are notable features of this landscape.[25]

A diverse range of chemical scaffolds is being pursued, predominantly targeting the cGAS enzymatic active site.[11] Key classes include indole derivatives (Novartis, Merck), quinolines (ImmuneSensor), benzofurans/benzothiophenes (Merck), benzofuran-pyrimidines (Roche), pyrido[4,3-b]indoles (Merck, Ventus), and thiazoles (BellBrook Labs).[13] Nitrogen-containing heterocycles are prevalent motifs. The rapid progression of orally available candidates like ImmuneSensor's IMSB-301 and Ventus Therapeutics' VENT-03 into Phase 1/2 clinical trials underscores the field's dynamism and the strategic focus on convenient administration for chronic diseases.[26]

Key challenges include translating potent biochemical inhibition into robust cellular activity and addressing species selectivity issues between human and mouse cGAS.[14] Freedom-to-operate (FTO) presents potential complexities due to foundational academic patents and overlapping scaffold claims among competitors.[13] Future innovation is expected to focus on optimizing pharmacokinetic properties, exploring novel mechanisms (e.g., allosteric or covalent inhibition, PROTACs), and potentially expanding into new therapeutic areas like neurodegeneration and fibrosis.[13]

Overall, the small molecule cGAS inhibitor field is a rapidly evolving and highly competitive area with significant therapeutic promise for treating debilitating autoimmune and inflammatory diseases. Success will require navigating a complex IP landscape and developing differentiated inhibitors with compelling clinical profiles.

## 2. Introduction

### 3.1 Background on cGAS: Role in Innate Immunity and Beyond

The innate immune system serves as the host's first line of defense against pathogen invasion and endogenous danger signals.[1] Central to this system are pattern recognition receptors (PRRs) that detect conserved microbial structures

(pathogen-associated molecular patterns, PAMPs) or host-derived molecules indicative of cellular stress or damage (damage-associated molecular patterns, DAMPs).[7] Among the most critical PRRs involved in detecting nucleic acids is cyclic GMP-AMP synthase (cGAS; gene symbol CGAS/MB21D1), identified as a major cytosolic DNA sensor.[1]

cGAS resides primarily in the cytoplasm and nucleus.[61] Its activation is triggered by the binding of double-stranded DNA (dsDNA) present in the cytosol, a compartment normally devoid of DNA in healthy cells.[2] This aberrant cytosolic dsDNA can originate from various sources, including invading pathogens (viruses, bacteria, parasites) or endogenous host sources such as damaged mitochondria (mtDNA), fragments of nuclear DNA leaking into the cytoplasm, DNA within micronuclei formed during genomic instability, or retrotransposon elements.[3] Notably, cGAS does not inherently discriminate between self and non-self DNA sequences, recognizing dsDNA based primarily on length (>45 base pairs) and structure.[5]

Upon binding dsDNA, cGAS undergoes conformational changes and oligomerization, activating its enzymatic function.[3] As a nucleotidyltransferase, activated cGAS utilizes cytosolic adenosine triphosphate (ATP) and guanosine triphosphate (GTP) to synthesize a unique cyclic dinucleotide, 2'3'-cyclic GMP-AMP (2'3'-cGAMP), which features both 2'-5' and 3'-5' phosphodiester linkages.[1]

This second messenger, 2'3'-cGAMP, diffuses through the cytoplasm and binds with high affinity to the adaptor protein STING (Stimulator of Interferon Genes; also known as TMEM173, MITA, ERIS, MPYS), which resides on the membrane of the endoplasmic reticulum (ER).[2] cGAMP binding induces a conformational change in STING, promoting its oligomerization and trafficking from the ER through the Golgi apparatus.[3] During trafficking, STING recruits and activates TANK-binding kinase 1 (TBK1).[1] Activated TBK1 phosphorylates the transcription factor Interferon Regulatory Factor 3 (IRF3).[1] Phosphorylated IRF3 dimerizes, translocates to the nucleus, and drives the transcription of type I interferons (IFN-α/β) and numerous IFN-stimulated genes (ISGs).[1] STING activation also triggers the NF-κB pathway, leading to the production of pro-inflammatory cytokines such

as Tumor Necrosis Factor (TNF), Interleukin-6 (IL-6), and IL-1β.[1] This coordinated response establishes an antiviral state and recruits other immune cells to combat infection or clear cellular debris.

Beyond its canonical role in innate immunity, cGAS activity is implicated in other cellular processes, including cellular senescence, DNA damage repair, apoptosis, autophagy regulation, and tumorigenesis, highlighting its broader physiological significance.[3]

### 3.2 Disease Relevance: Aberrant cGAS Activation in Autoimmunity and Inflammation

While crucial for host defense, the cGAS-STING pathway's inability to distinguish self from non-self DNA makes it a double-edged sword.[4] Under pathological conditions, the accumulation of self-DNA in the cytoplasm can lead to chronic, aberrant activation of the pathway, driving detrimental inflammation and contributing to the development of autoimmune diseases.[1] This can occur due to defects in nucleases responsible for clearing cytosolic DNA (e.g., TREX1, DNAse II), mitochondrial dysfunction leading to mtDNA release, or excessive DNA damage and genomic instability.[4]

The resulting sustained production of IFN-I and pro-inflammatory cytokines is a key pathogenic driver in several autoimmune and inflammatory disorders.[5] Examples include:

- **Systemic Lupus Erythematosus (SLE)**: Characterized by anti-dsDNA antibodies and elevated IFN-I signatures, SLE pathogenesis is strongly linked to aberrant cGAS-STING activation by self-DNA.[4]
- **Aicardi-Goutières Syndrome (AGS)**: A rare genetic interferonopathy often caused by mutations in genes like TREX1, leading to nucleic acid accumulation and constitutive cGAS-STING activation.[5] Knockout of cGAS rescues the lethal phenotype in TREX1-deficient mice, genetically validating cGAS as a target.[5]
- **STING-Associated Vasculopathy with onset in Infancy (SAVI)**: Caused by gain-of-function mutations in STING (TMEM173), leading to constitutive pathway activation.[7] While the defect is in STING, cGAS acts upstream, and inhibiting

cGAS could potentially mitigate the consequences.

- **Rheumatoid Arthritis (RA)**: Increased cytosolic dsDNA and cGAS expression are observed in synovial cells, correlating with disease severity.[4]
- **Other Conditions**: Evidence implicates aberrant cGAS-STING signaling in dermatomyositis, Sjogren's syndrome, systemic sclerosis, inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), non-alcoholic steatohepatitis (NASH), various fibrotic conditions (lung, liver, kidney), certain neurodegenerative diseases (ALS, Parkinson's, Alzheimer's, AMD), and complications of infections like COVID-19.[5]

The dual nature of the cGAS-STING pathway, being essential for defense but detrimental when chronically activated by self-DNA, presents a therapeutic challenge.[4] Strategies aim to either boost the pathway (using STING agonists) for cancer immunotherapy or anti-infective purposes, or inhibit the pathway (using cGAS or STING inhibitors) for autoimmune and inflammatory diseases.[9] This inherent complexity requires precise modulation and likely contributed to the timeline of therapeutic development, with focused efforts on inhibitors gaining momentum as the links to autoimmunity became clearer.

### 3.3 Significance of Small Molecule Inhibitors for cGAS

Given the central role of cGAS in initiating pathological inflammation in response to self-DNA, its inhibition represents a compelling therapeutic strategy for the aforementioned diseases.[5] Small molecules offer several potential advantages as cGAS inhibitors, particularly for chronic autoimmune and inflammatory conditions. Compared to biologics, small molecules typically possess better pharmacokinetic properties, including oral bioavailability and cell membrane permeability, allowing for convenient, systemic, long-term administration often required for these diseases.[64] The development of orally available cGAS inhibitors is a notable trend in the field, aiming to meet this need.[26]

Targeting cGAS, the initiating DNA sensor upstream of STING, may offer advantages in terms of specificity and safety compared to inhibiting downstream components like STING or TBK1.[7] cGAS inhibition directly prevents the production of cGAMP in response to cytosolic DNA. Inhibiting STING, while also effective,

might interfere with responses to bacterial cyclic dinucleotides (which can directly bind STING) or other potential STING-activating signals, potentially leading to broader immunosuppression.[10] Therefore, specific small molecule inhibitors of cGAS hold significant promise as targeted therapies to dampen pathological IFN-I production and inflammation in a range of debilitating diseases.

### 3.4 Objectives and Scope of this Review

The objective of this report is to provide a comprehensive patent landscape review focused specifically on **small molecule inhibitors of cGAS**. The analysis aims to map the intellectual property environment, identify key players and technologies, analyze chemical space and biological data disclosed in patents, assess competitive dynamics and FTO considerations, and identify potential future trends within defined parameters.

The scope of this review is strictly defined as follows:

- **Biological Target**: cGAS (cyclic GMP-AMP synthase)
- **Therapeutic Modality**: Small Molecule Inhibitors
- **Disease/Indication Focus**: Autoimmune disorders and inflammatory conditions where cGAS inhibition is therapeutically relevant.
- **Timeframe**: Patent documents published or granted from **2015 to Present** (reflecting the period of significant activity post-pathway elucidation).
- **Geographic Focus**: **US** (United States), **EP** (European Patent Office), **WO** (World Intellectual Property Organization - PCT applications), **CN** (China), and **JP** (Japan).
- **Patent Status**: Published patent applications and granted patents.
- **Small Molecule Sub-types**: Distinct chemical classes or scaffolds claimed as cGAS inhibitors.
- **Claim Types**: Prioritization of composition of matter claims, with consideration of relevant method of use claims for the specified diseases.

This review excludes biologics (e.g., antibodies, therapeutic proteins), STING agonists, cGAS activators, patents filed before 2015, and patents originating solely from jurisdictions outside the specified geographic scope.

## 4. Methodology

### 4.1 Simulated Search Strategy

This analysis is based on a simulated patent search performed on the extensive corpus of data the AI model was trained on, which includes patent documents, scientific literature, chemical databases, and other relevant textual information available up to the knowledge cutoff date. The process conceptually mimics a standard patent landscape search by identifying and analyzing documents relevant to the defined scope.

The core conceptual search logic involved identifying documents containing keywords and concepts related to:

- **Target**: "cGAS", "cyclic GMP-AMP synthase", "CGAS", "MB21D1"
- **Modality/Action**: "inhibitor", "antagonist", "small molecule", "compound"
- **Chemical Descriptors**: Specific chemical class terms (e.g., "indole", "quinoline", "pyrrolidine", "benzofuran", "pyridoindole", "thiazole") identified during iterative analysis.
- **Pathway Context**: "STING", "TMEM173", "interferon", "innate immunity", "inflammation", "autoimmune" (used for context and filtering).

Boolean operators (AND, OR, NOT) were conceptually applied to combine these terms and refine the document set. For instance, a core search concept would be (cGAS OR "cyclic GMP-AMP synthase") AND (inhibitor OR antagonist) AND ("small molecule" OR specific scaffold terms). Further filtering based on timeframe, geography, and exclusion criteria (e.g., NOT agonist, NOT biologic) was simulated. Given the close relationship between cGAS and STING, careful simulated filtering was applied to prioritize patents primarily focused on claiming novel small molecules asserted or demonstrated to inhibit cGAS directly, rather than those solely focused on downstream targets like STING where cGAS is mentioned only contextually.[13]

### 4.2 Data Sources

The analysis leverages information integrated from various sources present in the training data, including:

- **Public Patent Databases**: Representations of data from major patent offices such as the United States Patent and Trademark Office (USPTO), European Patent Office (EPO), World Intellectual Property Organization (WIPO), China National Intellectual Property Administration (CNIPA), and Japan Patent Office (JPO).
- **Scientific Literature**: Peer-reviewed journals (e.g., Nature, Science, Cell, Immunity, Journal of Medicinal Chemistry, ACS Medicinal Chemistry Letters, PLoS One, Frontiers journals) containing primary research, reviews, and structural/biological data related to cGAS and its inhibitors.[1]
- **Chemical Information**: Data pertaining to chemical structures (including SMILES representations where available), IUPAC names, and basic properties.
- **Other Sources**: Information potentially derived from news articles, company press releases, and public financial filings (e.g., SEC filings) available in the training data.[25]

It is crucial to reiterate that this analysis does not involve real-time access to live, proprietary patent databases (e.g., PatSnap Synapse, CAS SciFinder, Derwent Innovation, Cortellis) or external chemical informatics tools (e.g., RDKit, ChemDraw). The chemical structures, names, and associated data presented are representative examples based on the AI's learned knowledge and the provided snippets, not the output of a live, exhaustive search or structure generation software.



### 4.3 Conceptual Application of Keywords and Classification Codes

Keywords related to the target (cGAS, synonyms), action (inhibitor, antagonist), modality (small molecule), and relevant diseases (autoimmune, inflammation, SLE, AGS, etc.) were conceptually employed to identify relevant documents.

Furthermore, patent classification codes commonly associated with pharmaceuticals and relevant chemical structures were conceptually applied for filtering and categorization. These include, but are not limited to:

- **A61K 31/***: Medicinal preparations containing organic active ingredients. Subclasses specify heterocyclic compounds (e.g., A61K 31/40 for indoles,

A61K 31/47 for quinolines, A61K 31/41 for five-membered N-heterocycles, A61K 31/425 for thiazoles, A61K 31/505 for pyrimidines).[15]

- **C07D /***: Organic chemistry related to heterocyclic compounds, covering the synthesis and structure of various ring systems found in the inhibitors (e.g., C07D 209/* for indoles, C07D 215/* for quinolines, C07D 231/* for pyrazoles, C07D 249/* for triazoles, C07D 277/* for thiazoles, C07D 307/* for furans, C07D 471/*, C07D 487/*, C07D 491/* for fused systems).[13]
- **A61P /***: Codes indicating specific therapeutic activity, such as A61P 37/* (Drugs for immunological or allergic disorders), A61P 29/* (Antiinflammatory agents), A61P 25/* (Drugs for nervous system disorders, relevant for neuroinflammation aspects), A61P 35/* (Antineoplastic agents, relevant for potential dual roles or context).[13]

These classifications help conceptually group patents related to similar chemical matter or therapeutic intent.

### 4.4 Time Period Confirmation

The analysis covers patent documents and related information available within the training data corresponding to the period from **January 1, 2015, to the AI's last knowledge update**.

### 4.5 Geographic Coverage Confirmation

The analysis focuses on patent documents conceptually originating from or designating the following key jurisdictions: **US** (United States), **EP** (European Patent Office), **WO** (PCT applications), **CN** (China), and **JP** (Japan).

### 4.6 Inclusion/Exclusion Criteria Confirmation

The simulated analysis adhered to the following criteria:

- **Included**: Patents and published applications claiming or disclosing small molecule inhibitors of cGAS; documents published or granted between 2015 and the present; documents associated with US, EP, WO, CN, or JP jurisdictions; focus on autoimmune and inflammatory indications; consideration of composition of matter and relevant method of use claims.

- **Excluded**: Patents focused primarily on biologics [7], STING agonists, cGAS activators, patents with priority dates before 2015 (unless part of a family extending into the timeframe), patents solely from other jurisdictions, patents focused exclusively on non-therapeutic applications (e.g., diagnostic assays, research tools, unless disclosing novel inhibitors).

The reliance on static training data means the report reflects the landscape up to the knowledge cutoff date. Consequently, the very latest filings (within recent months) or real-time changes in legal status (e.g., recent grants, withdrawals, litigation outcomes) may not be captured. This limitation is particularly relevant for FTO assessments, which require validation through live database searches.

## 5. Overall Patent Landscape Overview

### 5.1 Trends in Patent Filing Activity (2015-Present)

Analysis of patent filings related to small molecule cGAS inhibitors within the specified scope (2015-present; US, EP, WO, CN, JP) reveals a marked increase in activity during this period. While the foundational discoveries of cGAS and its role occurred slightly earlier (around 2012-2013) [9], the translation into focused drug discovery efforts, particularly for inhibitors targeting autoimmune and inflammatory diseases, appears to have gained significant momentum from 2015 onwards. This surge likely correlates with the growing understanding of the pathway's dysregulation in human diseases like AGS and SLE, often linked to defects in nucleic acid metabolism (e.g., TREX1 deficiency) where cGAS knockout proved protective in preclinical models [5], and the increasing availability of structural information for cGAS to guide inhibitor design.[11]

Based on publication and priority dates observed in patent documents within the training data [13], the period from roughly 2017-2022 likely saw the peak of initial filings for distinct chemical scaffolds, reflecting intensive discovery efforts by multiple players entering the field. Recent publications and patent applications extending into 2023 and 2024 indicate that activity remains high, potentially shifting towards optimization of existing scaffolds, development of clinical candidates, and exploration of second-generation approaches or new chemical

matter.[13] The overall trend strongly suggests that cGAS inhibition is perceived as a high-value therapeutic strategy, attracting substantial R&D investment.

Table 1: Estimated Patent Filing Trend (Small Molecule cGAS Inhibitors, 2015-Present)
(Note: Counts are approximate, based on publication/priority dates in analyzed data, representing families with filings in US/EP/WO/CN/JP)

| **Year** | **Estimated Number of New Patent Families Published/Prioritized** | **Trend Notes** |
|---|---|---|
| 2015 | Low | Early activity, post-discovery phase |
| 2016 | Moderate | Increasing interest, initial filings emerge |
| 2017 | Moderate-High | Significant increase, key players active |
| 2018 | High | Peak activity likely reached |
| 2019 | High | Sustained high activity, diverse scaffolds |
| 2020 | High | Continued strong interest |
| 2021 | High | Ongoing filings, |

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| | | potential optimization focus |
| 2022 | Moderate-High | Continued activity, clinical candidates emerge |
| 2023+ | Moderate-High | Ongoing filings, focus likely on optimization/clinical |

### 5.2 Geographic Distribution of Patent Filings (US, EP, WO, CN, JP)

The geographic distribution of patent filings for small molecule cGAS inhibitors is concentrated in the major pharmaceutical markets. Analysis of patent documents indicates that the World Intellectual Property Organization (WO, representing PCT applications), the United States (US), and the European Patent Office (EP) are the dominant jurisdictions for filings.[13] This reflects the standard strategy of seeking broad protection in key commercial regions, often initiated via the PCT route.

Significant filing activity is also observed in China (CN) and Japan (JP), with many applicants pursuing national phase entry in these countries following PCT applications.[13] This underscores the perceived commercial importance of these Asian markets for potential autoimmune and inflammatory therapeutics. The strong overall contribution of US-based entities (both commercial and non-commercial) to patenting in related biomedical fields suggests the US is a primary hub for innovation in cGAS inhibitors as well.[107]

Table 2: Estimated Geographic Distribution Summary (Small Molecule cGAS Inhibitors, 2015-Present)
(Note: Percentages are approximate, based on filings within analyzed families across specified jurisdictions)

| Jurisdiction | Estimated % of Families with Filing | Notes |
|---|---|---|
| WO (PCT) | High (>75%) | Common starting point for international protection |
| US | High (>75%) | Key market, significant innovation origin |
| EP | High (>70%) | Key market |
| CN | Moderate-High (>50%) | Increasingly important market, consistent national phase entry |
| JP | Moderate-High (>50%) | Important market, consistent national phase entry |

### 5.3 Key Assignees/Companies

Several organizations have emerged as key players in the small molecule cGAS inhibitor patent landscape since 2015. These include a mix of large pharmaceutical companies, specialized biotechnology firms, and academic institutions that originated foundational IP. Based on the volume and significance of their patent filings within the scope of this review, the most prominent assignees include:

- **Novartis AG** [16]
- **Merck & Co. (and related entities)** [13]

- **Roche (F. Hoffmann-La Roche AG / Genentech, Inc.)** [13]
- **ImmuneSensor Therapeutics, Inc.** [20]
- **Ventus Therapeutics, Inc.** [21]
- **IFM Therapeutics, LLC / IFM Due, Inc.** (IP now largely with Novartis) [23]
- **BellBrook Labs, LLC** [15]
- **University of Texas System** (often co-assigned or licensed, particularly foundational IP) [17]
- **Pfizer Inc.** (Based on discovery of PF-06928215) [42]

Other academic institutions and smaller companies may also hold relevant patents, but these represent the most frequently identified assignees in the analyzed data.

### 5.4 General Observations on the Competitive Landscape

The landscape for small molecule cGAS inhibitors appears highly dynamic and competitive. The rapid emergence of multiple players following the validation of cGAS as a therapeutic target underscores the perceived value of this mechanism. There is a clear focus on developing inhibitors for chronic autoimmune and inflammatory diseases, driving the pursuit of orally bioavailable compounds.

Competition exists both in exploring diverse chemical matter and in optimizing specific scaffolds. While distinct chemical classes are being pursued by different entities, there are also areas of potential overlap, particularly around certain privileged scaffolds (e.g., substituted indoles, pyridoindoles). The interplay between academic discovery, biotech development, and large pharma investment (including M&A) is a defining characteristic of this field. The progression of candidates into clinical trials by companies like ImmuneSensor and Ventus signifies a maturation of the field, intensifying the competitive pressure and highlighting the importance of differentiation and robust IP protection.

## 6. Analysis by Assignee/Company

This section provides profiles of the most active companies and institutions identified in the small molecule cGAS inhibitor patent landscape, analyzing their portfolios and strategic focus within the defined scope (2015-Present; US, EP,

WO, CN, JP; autoimmune/inflammatory focus).

**Table 3: Key Assignees in Small Molecule cGAS Inhibition (2015-Present)**

| Assignee | Type | Estimated Relevant Families | Key Scaffolds Claimed | Notable Candidates/ Status |
|---|---|---|---|---|
| Novartis AG | Pharma | Moderate-High | Indole derivatives, Triazoles | Acquired IFM Due's STING antagonist program [25] |
| Merck & Co. | Pharma | Moderate-High | Pyrido[4,3-b]indoles, Benzofurans, Benzothiophenes, Indoles | Active R&D, STING agonist (MK-1454) also developed [33] |
| Roche (Genentech) | Pharma | Moderate-High | Benzofuran-pyrimidines linked to Proline derivatives | Potent cellular inhibitors disclosed [18] |
| ImmuneSensor Therapeutics | Biotech | Moderate | Quinoline derivatives | IMSB-301 (Oral, Phase 1 completed/o |

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|---|---|---|---|---|
| | | | | ngoing) [26] |
| Ventus Therapeutics | Biotech | Moderate | Pyrido[4,3-b]indoles, Oxoindolinyl amides (NLRP3) | VENT-03 (Oral, Phase 1 completed, Phase 2 planned) [38] |
| IFM Therapeutics / IFM Due | Biotech | Moderate | Indole ureas/squaramides (Primarily STING antagonists) | Acquired by Novartis [30] |
| BellBrook Labs | Biotech | Low-Moderate | Thiazole derivatives | Early-stage discovery [15] |
| University of Texas System | Academia | Moderate | Foundational cGAS/cGAMP IP, Quinoline derivatives (w/ IST) | Foundational research, licensing (e.g., to ImmuneSensor) [20] |
| Pfizer Inc. | Pharma | Low | Pyrazolopyrimidines | PF-06928215 (Tool compound, poor cell activity) [90] |

*(Note: "Estimated Relevant Families" is qualitative based on analyzed data; "Key Scaffolds" based on representative patents)*

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**Novartis AG**

- **Profile**: A global pharmaceutical company with extensive R&D capabilities across multiple therapeutic areas, including immunology and inflammation. Novartis has shown interest in the cGAS-STING pathway, evidenced by its collaboration with and subsequent acquisition of IFM Due, which focused on STING antagonists.[25]
- **Portfolio Analysis**: Novartis has filed patents claiming novel small molecule cGAS inhibitors, particularly focusing on indole derivatives substituted with various heterocyclic groups like pyrazoles and triazoles.[16] Their filings appear relatively recent within the 2015-present timeframe and cover major jurisdictions (US, EP, WO, CN, JP).
- **Strategic Focus**: The patents claim potent inhibition of cGAS (often in the low nM range biochemically) and target a broad range of inflammatory and autoimmune diseases, including SLE, AGS, Sjogren's, and vasculitis.[16] The focus seems to be on identifying best-in-class molecules through exploration of the indole scaffold. Their acquisition of IFM Due's STING program complements potential internal cGAS efforts, giving them assets targeting different nodes of the pathway.

**Merck & Co.**

- **Profile**: A major global pharmaceutical company with strong research programs in immunology, oncology, and infectious diseases. Merck has active programs targeting innate immunity, including the development of the STING agonist MK-1454 for immuno-oncology.[32]
- **Portfolio Analysis**: Merck has filed patents covering diverse chemical scaffolds as cGAS inhibitors, including pyrido[4,3-b]indoles, substituted benzofurans, benzothiophenes, and other indole derivatives.[13] Their filings span the key geographic regions.
- **Strategic Focus**: Merck's patents claim utility in a wide array of cGAS-related

diseases, including autoimmune conditions (SLE), inflammatory disorders, and notably, neurodegenerative diseases like Parkinson's, Alzheimer's, and ALS, suggesting an interest in CNS-penetrant inhibitors.[13] Their exploration of multiple distinct scaffolds indicates a broad discovery effort. The co-existence of STING agonist programs highlights their interest in modulating the pathway for different therapeutic contexts.

**Roche (F. Hoffmann-La Roche AG / Genentech, Inc.)**

- **Profile**: A leading global healthcare company strong in diagnostics and pharmaceuticals, with significant expertise in oncology and immunology.
- **Portfolio Analysis**: Roche/Genentech have filed patents focused on a distinct chemical class: benzofuran-pyrimidine derivatives linked to substituted proline moieties.[18] These filings cover the major jurisdictions. Their patents disclose extensive SAR data.
- **Strategic Focus**: The claimed compounds demonstrate potent biochemical and, importantly, cellular cGAS inhibition with good selectivity over downstream STING activation.[18] Roche patents explicitly mention prodrug strategies (methyl esters) to potentially improve properties.[18] Claimed indications include SLE, interferonopathies (AGS), fibrosing diseases (SSc, NASH, IPF), neurodegeneration (ALS, Parkinson's), and others, indicating broad therapeutic interest.[18] Their detailed disclosure of cellular activity and selectivity suggests a focus on developing clinically viable candidates.

**ImmuneSensor Therapeutics, Inc.**

- **Profile**: A clinical-stage biotechnology company specifically focused on developing modulators (inhibitors and agonists) of the cGAS-STING pathway. The company's technology originates from the foundational research of Dr. Zhijian J. Chen at the University of Texas Southwestern Medical Center, who played a key role in elucidating the pathway.[20]
- **Portfolio Analysis**: ImmuneSensor, often in collaboration with the University of Texas System, holds patents primarily focused on quinoline-based cGAS inhibitors.[20] Their portfolio includes filings in major jurisdictions.
- **Strategic Focus**: ImmuneSensor is clearly focused on translating their cGAS

inhibitors into clinical therapies for inflammatory and autoimmune diseases. Their lead candidate, IMSB-301, is an orally available small molecule cGAS inhibitor that has completed/is in Phase 1 trials in healthy volunteers, with plans to move into patient studies for AGS and SLE.[26] Preclinical data showed efficacy in models of AGS and inflammatory arthritis.[26] Their strategy appears centered on leveraging deep pathway knowledge to develop potentially best-in-class oral inhibitors.

**Ventus Therapeutics, Inc.**

- **Profile**: A clinical-stage biotechnology company utilizing its proprietary structure-based drug discovery platform (ReSOLVE®) to target challenging proteins in immunology, inflammation, and neurology.[38]
- **Portfolio Analysis**: Ventus has patent filings covering small molecule modulators, including cGAS inhibitors based on pyrido[4,3-b]indole scaffolds.[21] They also have programs targeting NLRP3.[29] Their filings cover key territories.
- **Strategic Focus**: Ventus aims to develop potent and selective oral inhibitors. Their lead cGAS inhibitor, VENT-03, discovered using their platform, has successfully completed Phase 1 studies demonstrating safety, tolerability, and a PK profile suitable for once-daily dosing.[38] They plan to initiate a Phase 2 trial in lupus patients in 2025 and are exploring other potential indications.[38] Their focus on structural biology and computational tools likely drives their scaffold selection and optimization strategy.[38]

**IFM Therapeutics, LLC / IFM Due, Inc.**

- **Profile**: IFM Therapeutics is a biotech company focused on innate immunity targets. They established IFM Due as a subsidiary specifically to develop antagonists of the cGAS-STING pathway for inflammatory diseases, leveraging expertise from co-founder Andrea Ablasser.[25]
- **Portfolio Analysis**: IFM Due generated patents primarily focused on STING antagonists derived from the H-151 scaffold (indole ureas, squaramides, oxalamides).[75] While primarily targeting STING, this work is highly relevant to the pathway.

- **Strategic Focus**: IFM Due's strategy was to develop orally available STING antagonists for a range of inflammatory conditions.[25] This culminated in a collaboration and subsequent acquisition of IFM Due by Novartis in early 2024, transferring the rights to this portfolio.[30]

**BellBrook Labs, LLC**

- **Profile**: A company providing drug discovery tools and services, which has also engaged in internal drug discovery efforts.
- **Portfolio Analysis**: BellBrook Labs has patents claiming thiazole derivatives as cGAS inhibitors/antagonists.[15]
- **Strategic Focus**: Their patents suggest an early-stage discovery program targeting cGAS for inflammatory and autoimmune diseases. The specific stage of development or clinical translation plans are less clear compared to dedicated therapeutic companies.

**University of Texas System**

- **Profile**: A major US public university system encompassing UT Southwestern Medical Center, where the cGAS-STING pathway was significantly elucidated by Zhijian J. Chen's group.[9]
- **Portfolio Analysis**: Holds foundational patents related to cGAS, cGAMP, and the pathway itself.[19] They are also co-assignees on later patents covering specific inhibitors, notably the quinoline series developed with ImmuneSensor Therapeutics.[20]
- **Strategic Focus**: As an academic institution, their focus is on fundamental research and discovery, with subsequent translation often occurring via licensing to biotech or pharmaceutical companies, as exemplified by the ImmuneSensor collaboration. Their early IP forms a critical part of the landscape.

**Pfizer Inc.**

- **Profile**: A leading global pharmaceutical company.
- **Portfolio Analysis**: Pfizer researchers published the discovery of PF-06928215, a pyrazolopyrimidine cGAS inhibitor identified via HTS and

fragment screening.[90]

- **Strategic Focus**: While PF-06928215 demonstrated high biochemical affinity (Kd 200 nM), it reportedly lacked cellular activity.[18] Its primary contribution appears to be as a high-affinity tool compound and proof-of-concept for active site inhibition. The extent of Pfizer's ongoing strategic commitment to cGAS *inhibitors* based solely on this publication is unclear.

Emerging Players

Identifying truly "emerging" players solely from the provided patent snippets is challenging. However, the continued filing activity suggests that other companies or academic groups beyond those listed above may be active at earlier stages. Monitoring new patent publications and scientific literature from key academic labs remains important for identifying new entrants.

The differing strategies observed – broad exploration by pharma versus focused clinical drives by biotechs, often built on academic IP – reflect the typical dynamics of drug discovery. The licensing of foundational IP from institutions like the University of Texas to biotechs like ImmuneSensor highlights the critical role of academic research in seeding this field and the importance of technology transfer for clinical development.

## 7. Competitive Analysis

### 7.1 Comparison of Key Player Portfolios

The patent portfolios of the key players in the small molecule cGAS inhibitor space exhibit distinct characteristics:

- **Portfolio Size and Recency**: Large pharma companies like Novartis, Merck, and Roche appear to have moderately sized but growing portfolios specifically focused on cGAS inhibitors within the 2015-present timeframe, often building upon broader expertise in immunology. Biotechs like ImmuneSensor and Ventus have portfolios that seem highly focused on their lead cGAS inhibitor programs, likely initiated based on foundational IP or platform technology, with filings potentially concentrated around their specific chemical matter and clinical candidates. The University of Texas holds older, foundational IP related to the pathway itself, plus newer, co-assigned IP on specific inhibitors

developed with partners like ImmuneSensor.

- **Technical Focus**: There is significant diversity in the chemical scaffolds being pursued. Novartis focuses on indoles [16], Merck explores multiple classes including pyridoindoles and benzofurans/thiophenes [13], Roche concentrates on benzofuran-pyrimidines linked to prolines [18], ImmuneSensor on quinolines [20], Ventus on pyridoindoles [21], and BellBrook on thiazoles.[17] Most efforts appear directed towards inhibiting the cGAS enzymatic active site [11], although some patents mention targeting DNA binding or dimerization.[7]

### 7.2 Strategic Patenting Approaches

Analysis of patent documents suggests varied strategic approaches:

- **Claim Breadth**: Early patents, particularly those originating from academia, may contain broader conceptual claims. Industry patents often feature extensive Markush structures defining a chemical space around a core scaffold, aiming for broad coverage, but granted claims may be narrower. Patents covering clinical candidates (e.g., potentially related to IMSB-301 or VENT-03) might have narrower claims focused on specific structures and their properties.
- **Filing Speed and Geography**: Most players utilize the PCT system for initial broad filing, followed by national/regional phase entry into key markets (US, EP, CN, JP), indicating a standard global strategy.[13] The consistent entry into CN and JP suggests these are considered important future markets. Filing frequency appears high across the board, especially between ~2017-2022, reflecting intense R&D activity.
- **Claim Type Focus**: Composition of matter claims covering novel chemical entities are universally prioritized, forming the core protection. Method of use claims targeting specific autoimmune/inflammatory diseases (SLE, AGS, RA, NASH, neuroinflammation etc.) are also common, defining the intended therapeutic applications.[13] Claims related to specific properties like oral bioavailability or formulations are less prominent in the initial discovery patents but are likely pursued in later-stage filings or as trade secrets.

### 7.3 Areas of Patent Density and Potential Overlap

The chemical space around certain scaffolds shows higher density and potential for overlap. Notably, the **pyrido[4,3-b]indole** scaffold appears in patents from both Merck and Ventus Therapeutics.[13] This convergence suggests this core structure is particularly promising for achieving cGAS inhibition but also creates a crowded IP landscape around it. Navigating FTO within this specific chemical space likely requires careful analysis of claim scope, substitution patterns, and priority dates. Other areas involving substituted indoles might also see density given the activity of Novartis and Merck in this area. This highlights the importance for competitors to clearly differentiate their compounds, potentially through unique substitution patterns, improved properties, or alternative mechanisms of action.

### 7.4 Identification of Potential White Space

Despite the intense activity, potential white spaces or less crowded areas may exist:

- **Novel Chemical Scaffolds**: While several heterocyclic systems are heavily explored, there might be opportunities for genuinely novel, structurally distinct scaffolds that inhibit cGAS.
- **Alternative Mechanisms**: The majority of efforts focus on the catalytic site. Targeting cGAS-DNA interaction [7], cGAS dimerization [35], or allosteric sites could represent less crowded mechanistic approaches. Developing degraders (e.g., PROTACs) specifically for cGAS is another potential avenue, although early examples target downstream proteins.[42]
- **Specific Therapeutic Niches**: While broad autoimmune indications like SLE are common targets, focusing on less frequently mentioned but biologically rational indications (e.g., specific fibrotic conditions, subtypes of neuroinflammation requiring specific properties like CNS penetration) might offer less direct IP competition.
- **Geographic Gaps**: While major markets are well-covered, specific smaller jurisdictions might have less dense patent coverage, although commercial viability would need assessment.

### 7.5 Patenting Trends by Key Company (2015-Present)

- **University of Texas**: Early foundational filings pre-date or overlap the start of the 2015 timeframe, with later co-assigned filings (e.g., with ImmuneSensor) appearing more recently.
- **Large Pharma (Novartis, Merck, Roche)**: Appear to have initiated focused cGAS inhibitor programs within the 2015-present timeframe, with filings becoming more frequent from ~2017/2018 onwards, indicating ramped-up discovery efforts.
- **Biotechs (ImmuneSensor, Ventus)**: Likely initiated filings based on licensed IP or platform discoveries within the 2017-2020 period, followed by filings potentially focused on lead optimization and clinical candidates more recently.
- **IFM Due**: Activity concentrated in the period following its formation (~2019) until its acquisition by Novartis (~2024), primarily focused on STING antagonists.

Overall, the timeline suggests academic groundwork followed by significant industry investment and focused development within the last 5-8 years.

### 7.6 Collaborations, Licensing, and Litigation

- **Licensing**: The relationship between the University of Texas System and ImmuneSensor Therapeutics is a clear example of academic discovery licensed for commercial development.[20] Similar foundational links likely exist between IFM Therapeutics/IFM Due and academic founders like Andrea Ablasser.[24]
- **Collaboration & Acquisition**: The collaboration between Novartis and IFM Due, culminating in Novartis acquiring IFM Due and its STING antagonist portfolio, is a major strategic event in the broader cGAS-STING pathway landscape.[25] This highlights the value placed on modulators of this pathway and the role of M&A in consolidating assets.
- **Litigation**: No specific instances of litigation related to small molecule cGAS inhibitors were identified in the analyzed data. However, given the competitive landscape and potential scaffold overlap, future litigation cannot be ruled out, particularly as candidates advance towards commercialization.

## 8. Analysis of Claimed Chemical Space

### 8.1 Detailed Examination of Claimed Structures

The patent landscape reveals a rich and diverse chemical space being explored for small molecule cGAS inhibitors. Analysis of patents from key players like Novartis, Merck, Roche, ImmuneSensor, Ventus, and BellBrook Labs indicates a strong focus on heterocyclic scaffolds. Common structural features include:

- **Core Scaffolds**: Predominantly nitrogen-containing fused or single heterocyclic systems. Frequently observed cores include:
  - **Indoles**: Often substituted at positions 1, 2, 3, 5, 6, and 7.[13]
  - **Pyrido[4,3-b]indoles**: A tricyclic system appearing in patents from Merck and Ventus.[13]
  - **Quinolines**: Substituted quinoline derivatives are pursued by ImmuneSensor.[20]
  - **Benzofurans / Benzothiophenes**: Often fused or linked to other heterocycles like pyrimidines or piperidines.[13]
  - **Pyrazolopyrimidines**: The scaffold of the Pfizer tool compound PF-06928215.[90]
  - **Thiazoles**: Explored by BellBrook Labs.[17]
  - **Proline Derivatives**: Used as a key component linked to benzofuran-pyrimidines by Roche.[18]
- **Key Substituents**: Halogens (F, Cl, Br), alkyl (methyl, ethyl), alkoxy (methoxy), trifluoromethyl (CF3), cyano (CN), hydroxyl (OH), amino (NH2), carboxylic acid (COOH), esters, amides, and various small heterocyclic rings (pyrazoles, triazoles, pyridines, piperidines, pyrrolidines) are commonly employed as substituents to modulate potency, selectivity, and physicochemical properties.
- **Linkers**: In some scaffolds, linkers (e.g., alkyl chains, ether linkages, amide bonds) connect different parts of the molecule, such as linking a core heterocycle to a terminal functional group like a carboxylic acid.[18]

### 8.2 Common Chemical Classes and Motifs

Nitrogen-containing heterocycles are overwhelmingly prevalent, likely reflecting

their ability to form key interactions (hydrogen bonds, π-stacking) within the cGAS active site or other binding pockets, and their versatility in modulating drug-like properties. Common motifs include:

- Fused heterocyclic systems (indoles, quinolines, benzofurans, pyridoindoles).
- 5-membered N-heterocycles (pyrazoles, triazoles, imidazoles) often appended to core scaffolds.
- 6-membered N-heterocycles (pyridines, pyrimidines, piperidines).
- Presence of hydrogen bond donors/acceptors (OH, NH, C=O, heterocyclic N).
- Presence of halogens or CF3 groups, likely for modulating electronics, binding, or metabolic stability.
- In several series, a terminal carboxylic acid group, potentially important for binding or added via a prodrug strategy.[18]

The frequent appearance of these motifs across different assignee portfolios suggests their general importance for achieving cGAS inhibition within the small molecule space explored so far.

### 8.3 Representative Key Chemical Structures

*(Note: Chemical structure images cannot be generated. Textual descriptions, SMILES, and IUPAC names are provided where available/inferable from snippets).*

1. **G150 (Roche/Academia)** [11]
   - **Description**: A pyrido[4,3-b]indole core substituted with chlorine, fluorine, methyl, and hydroxyl groups, with a 2-hydroxyethanone moiety attached to the piperidine nitrogen. Specifically binds the cGAS active site.
   - **SMILES (Inferred)**: CC1=C2C(C(Cl)=C(F)C=C2N1C3CCN(C(=O)CO)CC3)=CC=C1 (Exact structure may vary slightly based on full publication)
   - **IUPAC (Inferred)**: 1-(7-Chloro-6-fluoro-9-hydroxy-5-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-2-hydroxyethanone [13]
2. **PF-06928215 (Pfizer)** [18]
   - **Description**: A pyrazolo[1,5-a]pyrimidine core substituted with phenyl and hydroxyl groups, linked via an amide bond to a (1R,2S)-2-aminocyclohexanecarboxylic acid moiety. Binds the cGAS active site.

- **SMILES**: OC(=O)[C@H]1CCCC[C@H]1NC(=O)C2=C3N(N=C2)C(O)=CC(C4=CC=CC=C4)=N3 [90]
- **IUPAC**: (1R,2S)-2-[[(7-hydroxy-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)carbonyl]amino]-cyclohexanecarboxylic acid [90]

3. **Novartis Indole Example (Representative from EP4267564A1)** [16]
   - **Description**: A 1H-indole core substituted at C2 with a trifluoromethyl-triazole, at C3 with a pyrazole, and variously substituted at positions 1, 5, 6, and 7 (e.g., methyl, methoxy, chloro, fluoro).
   - **SMILES (Example: 6-chloro-7-fluoro-5-methoxy-1-methyl-3-(1H-pyrazol-4-yl)-2-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-indole)**: COC1=C(F)C(Cl)=C2C(=C1)C(C3=CNC=N3)=C(N2C)C4=NN=C(N4)C(F)(F)F (Inferred)
   - **IUPAC (Example)**: 6-chloro-7-fluoro-5-methoxy-1-methyl-3-(1H-pyrazol-4-yl)-2-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H-indole [16]
4. **Roche Benzofuran-Pyrimidine-Proline Example (Representative from AU2022273980A1)** [18]
   - **Description**: A (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid core N-substituted with a 4-(trifluoromethyl)benzofuro[3,2-d]pyrimidine moiety, which is further linked via a pyridine ring bearing substituents (e.g., F, OMe, and a substituted oxane ring).
   - **SMILES (Example 1.01 - Complex, partial description)**: Structure involves the core (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid linked to 4-(trifluoromethyl)-8-oxa-3,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaene via a substituted pyridine linker. (Full SMILES not readily available from snippet).
   - **IUPAC (Example 1.01)**: (2S,4S)-4-hydroxy-1-(4-(trifluoromethyl)-8-oxa-3,5-diazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaen-11-yl)-N-((S)-1-(2-methoxy-6-(((3R,5R)-5-methyl-1,4-dioxan-3-yl)methoxy)pyridin-3-yl)ethyl)pyrrolidine-2-carboxamide (From full patent text, complex).
5. **ImmuneSensor Quinoline Example (Representative from US12091387B2)** [20]
   - **Description**: A quinoline core, often dichloro- or bromo-substituted at C7/C8, bearing a triazole or similar heterocycle at C4, and linked at C2 to

an (S)-pyrrolidine ring which is further functionalized with a methoxypropanoic acid side chain.

- **SMILES (Example I-903)**: O=C(O)CCOC[C@H]1CCCN1C2=NC3=C(C=C(Cl)C(Cl)=C3)C=C2C4=CN=NN4 (Inferred)
- **IUPAC (Example I-903)**: (S)-3-((1-(7,8-dichloro-4-(1H-1,2,3-triazol-1-yl)quinolin-2-yl)pyrrolidin-2-yl)methoxy)propanoic acid [20]

**Table 4: Representative Claimed Chemical Structures for cGAS Inhibition**

| Assignee | Patent Example/ID | Textual Description | Representative Structure (SMILES/IUPAC if available) | Claimed Target Site |
|---|---|---|---|---|
| Roche/Academia | G150 | Pyrido[4,3-b]indole core with hydroxyethanone side chain | IUPAC (Inferred): 1-(7-Chloro-6-fluoro-9-hydroxy-5-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-2-hydroxyethanone | Active Site [11] |
| Pfizer | PF-06928215 | Pyrazolo[1,5-a]pyrimidine | SMILES: OC(=O)[C@H | Active Site [93] |

| | | | | |
|---|---|---|---|---|
| | | linked to aminocyclohexanecarboxylic acid | ]1CCCC[C@H]1NC(=O)C2=C3N(N=C2)C(O)=CC(C4=CC=CC=C4)=N3 IUPAC: (1R,2S)-2-[[(7-hydroxy-5-phenylpyrazolo[1,5-a]pyrimidin-3-yl)carbonyl]amino]-cyclohexane carboxylic acid [90] | |
| Novartis | EP4267564A1 Example | Substituted 1H-indole with triazole at C2, pyrazole at C3 | IUPAC (Example): 6-chloro-7-fluoro-5-methoxy-1-methyl-3-(1H-pyrazol-4-yl)-2-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-1H- | cGAS (Mechanism not specified) |

| | | | | |
|---|---|---|---|---|
| | | | indole [16] | |
| Roche | AU2022273980A1 Example 1.01 | Benzofuro[3,2-d]pyrimidine linked via pyridine to substituted 4-hydroxyproline | (See description above; full structure complex) | cGAS (Mechanism not specified) |
| ImmuneSensor | US12091387B2 Example I-903 | Dichloroquinoline linked at C2 to pyrrolidine-methoxypropanoic acid, triazole at C4 | IUPAC: (S)-3-((1-(7,8-dichloro-4-(1H-1,2,3-triazol-1-yl)quinolin-2-yl)pyrrolidin-2-yl)methoxy)propanoic acid [20] | cGAS (Mechanism not specified) |
| Ventus | WO2019153002A1 Example | Pyrido[4,3-b]indole core with hydroxyethanone side chain | General structure: 1-(3,4-Dihydro-1H-pyrido[4,3-b]indol- | cGAS (Mechanism not specified) |

| | | | | |
|---|---|---|---|---|
| | | | 2(5H)-yl)-2-hydroxyethanone derivatives [21] | |
| BellBrook | WO2017176812A1 Example | Thiazole-based heterocyclic scaffold | General Formula I derivatives [17] | cGAS (Mechanism not specified) |

### 8.4 Analysis of Markush Structures

Patents in this field frequently employ broad Markush claims to cover a wide chemical space around a core scaffold. For example, Novartis' EP4267564A1 defines Formula I with multiple variable points (R1-R8, X) allowing for numerous combinations of substituents, including various alkyl, haloalkyl, cycloalkyl, aryl, and heteroaryl groups at different positions on the indole and attached heterocycles.[16] Similarly, Merck's WO2023154962A1 uses Formula (I) and (II) with variables (R1-R7) encompassing diverse functional groups and ring systems attached to indole, benzofuran, or benzothiophene cores.[13] Roche's patents define variables around their proline-linked benzofuran-pyrimidine core.[18] These broad claims aim to protect not only the specifically synthesized examples but also structurally related analogues, defining the proprietary chemical space for each assignee. The breadth of these claims often reflects the stage of discovery, with earlier filings potentially having wider scope than later filings focused on optimized candidates. Analyzing the specific definitions within these Markush structures is crucial for understanding the boundaries of each player's claimed territory and identifying potential FTO issues or remaining white space. The use of prodrug strategies, as seen in the Roche patent [18], adds another layer, potentially covering ester or other cleavable derivatives of the active carboxylic acid compounds, further expanding the protected chemical space.

### 8.5 Potential Approaches for Visualization

Visualizing the claimed chemical space effectively would typically involve computational cheminformatics approaches (beyond AI capabilities). Methods could include:

- **Scaffold Clustering**: Grouping claimed compounds based on their core molecular frameworks to identify the main structural themes pursued by different assignees.
- **Chemical Similarity Mapping**: Using techniques like t-distributed Stochastic Neighbor Embedding (t-SNE) or Principal Component Analysis (PCA) based on molecular fingerprints to map the chemical diversity and identify clusters of similar compounds and potentially unoccupied regions (white space).
- **Property Distribution Analysis**: Plotting key physicochemical properties (e.g., molecular weight, lipophilicity (logP), polar surface area) for claimed compounds to understand the property space being explored and identify potential gaps or areas associated with better drug-like characteristics.

Such visualizations would provide a powerful overview of the competitive chemical landscape and guide future design efforts.

## 9. Structure-Activity Relationship (SAR) Insights from Patents

### 9.1 Disclosed Biological Data

Patents and associated publications provide valuable, albeit sometimes incomplete, biological data linking specific chemical structures to cGAS inhibitory activity. Key data types include:

- **Biochemical Inhibition (IC50/Kd)**: Many patents report IC50 values from *in vitro* assays measuring direct inhibition of cGAS enzymatic activity (cGAMP production). Examples include:
  - G150: IC50 reported for human cGAS.[11] Roche publication details IC50s for G-chemotype inhibitors against human and mouse cGAS.[14]
  - PF-06928215: IC50 = 4.9 µM (FP assay), Kd = 200 nM (SPR).[90]
  - Novartis (EP4267564A1): Claims compounds with activity <= 30 µM, Table 1 provides activity categories (A, B, C) likely corresponding to IC50 ranges.[16]

- Roche (AU2022273980A1): Provides specific hcGAS IC50 values for numerous examples, often in the low nM range (e.g., 5 nM for Ex 1.01).[18]
- Merck (WO2023154962A1): Table 2 provides % inhibition categories (+, ++, +++) for compounds against h-cGAS and m-cGAS.[13]
- BellBrook (WO2017176812A1): Provides activity categories (A, B, C) for biochemical IC50s.[17]
- Other inhibitors like CU-32 (0.66 µM) and CU-76 (0.27 µM) also have reported IC50s.[18]

- **Cellular Activity (EC50/IC50)**: Assessing inhibition in cellular models (e.g., blocking IFN/ISG production in response to DNA stimulation in THP-1 cells or primary cells) is crucial. Examples include:
  - Roche (AU2022273980A1): Reports THP1(vir) IC50 values (cellular potency) and THP1(cGAMP) IC50 values (selectivity vs. downstream STING), with many examples showing THP1(vir) IC50 < 1 µM and good selectivity ratios.[18] Also reports hWB IC50 (human whole blood assay).
  - CU-32/CU-76: Reported to selectively inhibit the DNA pathway in human cells.[35]
  - Merck (WO2023154962A1): Table 3 provides cellular activity data (% viability, IFN/NF-κB inhibition categories) in THP1 cells.[13]
  - PF-06928215: Notably reported to have poor cellular activity despite biochemical potency.[18] Early fragment hits also lacked cell activity.[12]
- **Binding Mode/Target Engagement**: Structural data (co-crystal structures) or biophysical methods (SPR, thermal shift) confirm direct binding.
  - G150: Co-crystal structure shows binding in active site.[11] Roche publication provides detailed structural insights.[14]
  - PF-06928215: Structural data available (PDB 5V8N).[92] SPR confirmed binding.[42]
  - Roche (AU2022273980A1): Mentions structural insights guided design.[14]
  - STING inhibitors (context): Thermal shift assays used for STING agonists/antagonists.[78]

**Table 5: Summary of Representative Disclosed SAR Data for cGAS Inhibitors**

| Assignee/ Ref | Compound/Scaffold | Assay Type | Target | Potency | Key SAR Notes |
|---|---|---|---|---|---|
| Roche/Academia [11] | G150 (Pyridoindole) | Biochemical IC50 | h-cGAS | Potent (nM range inferred) | Active site binder; SAR explored around core. Shows species selectivity. |
| Pfizer [90] | PF-06928215 (Pyrazolopyrimidine) | Biochemical IC50 / Kd | h-cGAS | 4.9 µM / 200 nM | High affinity active site binder. |
| Pfizer [18] | PF-06928215 | Cellular Activity | h-cGAS pathway | Poor / Inactive | Example of in vitro/cellular disconnect. |
| Novartis [16] | Indole derivative | Biochemic | h-cGAS | <= 30 µM (Categorie | SAR explored |

| | | | | | |
|---|---|---|---|---|---|
| | s | al IC50 | | s A,B,C) | via substituti ons on indole and appended heterocycl es. |
| Roche [18] | Benzofura n-pyrimidin e-proline | Biochemic al IC50 | h-cGAS | Often low nM (e.g., 5 nM) | Potent biochemic al inhibition. |
| Roche [18] | Benzofura n-pyrimidin e-proline | Cellular IC50 (THP1vir) | h-cGAS pathway | Often < 1 µM (e.g., 530 nM) | Good cellular potency achieved. |
| Roche [18] | Benzofura n-pyrimidin e-proline | Cellular IC50 (THP1cGA MP) | STING pathway | High µM / >10 µM | Demonstr ates selectivity for cGAS over downstre am STING. |
| Roche [18] | Ester Prodrugs (P01-P03) | Biochemic al IC50 | h-cGAS | > 7000 nM | Carboxyl group essential for |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | biochemical activity. |
| Roche [18] | Ester Prodrugs (P01-P03) | Cellular IC50 (THP1vir) | h-cGAS pathway | Sub-µM / low µM | Retained cellular activity, suggesting intracellular hydrolysis. |
| Merck [13] | Various (Indoles, Benzofurans etc.) | Biochemical %Inh | h-cGAS, m-cGAS | Categories (+, ++, +++) | Broad screening data across scaffolds. |
| Merck [13] | Various | Cellular Activity | h-cGAS pathway | Categories (+, ++, +++) | Cellular activity assessed in THP1 cells. |
| ImmuneSensor [20] | Quinoline derivatives | (Data not specified in snippet) | cGAS | (Data not specified in snippet) | Lead candidate IMSB-301 implies potent compoun |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | ds exist. |
| Ventus [21] | Pyrido[4,3-b]indole derivatives | (Data not specified in snippet) | cGAS | (Data not specified in snippet) | Lead candidate VENT-03 implies potent compounds exist. |
| BellBrook [17] | Thiazole derivatives | Biochemical IC50 | cGAS | Categories (A, B, C) | Early discovery data. |
| Lama et al. [35] | CU-32 / CU-76 (Triazine) | Biochemical IC50 | hcGAS | 0.66 µM / 0.27 µM | Active site inhibitors with cellular activity. |

### 9.2 Inferred SAR and Key Structural Features

Based on the claimed structures and available data, several SAR trends can be inferred:

- **Active Site Binding**: The success of compounds like G150 and PF-06928215, along with structural work [11], confirms the druggability of the ATP/GTP binding site. Key interactions likely involve hydrogen bonding (e.g., with Ser434, Tyr248 in G150 [11]) and hydrophobic/π-stacking interactions (e.g., with Tyr436, Phe488, Leu490 in G150 [11]; pocket involving Tyr436/His437 for PF-06928215 derivatives [42]). The prevalence of N-heterocycles likely facilitates these interactions.
- **Importance of Specific Substituents**: The specific nature and position of

substituents on the core scaffolds are critical. For example, in Novartis' indoles, substitutions at C2, C3, C5, C6, and C7 seem important.[16] In ImmuneSensor's quinolines, C2, C4, C7, and C8 substitutions are key.[20] For Roche's compounds, the specific proline stereochemistry and substituents on the pyridine linker influence activity.[18]

- **Role of Carboxylic Acids/Prodrugs**: The presence of a carboxylic acid in several promising series (Roche, ImmuneSensor, Pfizer) suggests it may form crucial interactions (e.g., salt bridge, H-bonds). However, this group can impair permeability, leading to the exploration of prodrugs (e.g., Roche's esters [18]) to improve cellular activity or oral PK. This highlights the challenge of balancing potency with drug-like properties.
- **Cellular Activity Optimization**: Achieving good cellular potency (e.g., THP1(vir) IC50) requires optimization beyond just biochemical inhibition. Factors like cell permeability, efflux susceptibility, and intracellular stability become critical. The successful development of compounds with low nM biochemical IC50s and sub-µM cellular IC50s (e.g., by Roche [18]) demonstrates that this gap can be bridged through careful medicinal chemistry optimization.
- **Species Selectivity**: The discovery that a single amino acid difference (Thr vs. Ile) between human and mouse cGAS active sites can drastically alter inhibitor potency for certain chemotypes [14] is a significant finding. This necessitates careful consideration during lead optimization and preclinical testing. Compounds with potent activity against both species are highly desirable for translational studies, or alternative models (e.g., humanized mice) may be required. Roche's effort to engineer dual-species inhibitors addresses this challenge directly.[14]

### 9.3 Key Structural Features for Potency and Selectivity

- **Potency Drivers**: Interactions within the hydrophobic pockets and hydrogen bonding networks of the active site appear crucial. The specific arrangement of heterocyclic rings and functional groups determines the binding affinity.
- **Selectivity Features**: Selectivity over downstream STING activation is demonstrated by compounds showing potent inhibition in DNA-stimulated

cellular assays (e.g., THP1(vir)) but weak activity in cGAMP-stimulated assays (e.g., THP1(cGAMP)).[18] This indicates the compounds act upstream at cGAS. Selectivity against other nucleotidyltransferases or kinases would also be important but is less frequently reported in these initial patent disclosures.

## 10. Disclosed Synthetic Methodologies

### 10.1 Representative Synthetic Routes and Key Intermediates

Patent documents provide substantial detail on the synthetic routes used to prepare the claimed small molecule cGAS inhibitors. These routes typically involve multi-step sequences leveraging standard organic chemistry transformations to construct the often complex heterocyclic core structures and introduce necessary substituents.

- **Novartis Indoles (EP4267564A1)**: Synthesis involves building the indole core via Sonogashira coupling followed by cycloisomerization, or via enamine formation and intramolecular Heck coupling. Key intermediates include halogenated anilines, indole-2-carboxylates, and various functionalized bromo-triazoles. Suzuki and Ullmann couplings are used to append heterocycles.[16]
- **Merck Scaffolds (WO2023154962A1)**: Routes for pyrido[4,3-b]indoles involve amide couplings, cyclizations, and Suzuki reactions on indole precursors. Benzofuran synthesis uses boronylation, reaction with N-hydroxyphthalimide, coupling with tetrahydropyridone, triflate formation, and Suzuki coupling. Benzothiophene and pyridoimidazole syntheses follow analogous logic using relevant starting materials and intermediates.[13] Key intermediates include Boc-protected amines, boronic esters/acids, triflates, and various heterocyclic building blocks.
- **Roche Benzofuran-Pyrimidines (AU2022273980A1)**: Synthesis relies on coupling a substituted chloro-pyrimidine intermediate with a specific (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid derivative. The pyrimidine intermediate itself is synthesized from benzofuran precursors. The pyridine linker component is often built using organometallic chemistry (Grignard or organolithium addition to ketones).[18] Numerous functionalized pyridine,

pyrrolidine, and benzofuran intermediates are detailed.

- **ImmuneSensor Quinolines (US12091387B2)**: Exemplified routes involve building the substituted quinoline core, followed by coupling with a pyrrolidine derivative (often via amide formation and reduction or direct SNAr), and subsequent functionalization (e.g., introduction of triazole at C4, elaboration of the side chain on pyrrolidine N to include the propanoic acid moiety).[20] Key intermediates include substituted quinoline precursors and chiral pyrrolidine building blocks.
- **Ventus Pyrido[4,3-b]indoles (WO2019153002A1)**: Synthesis focuses on constructing the 1-(3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-2-hydroxyethanone structure. Details involve building the tricyclic core and attaching the hydroxyethanone side chain.[21]
- **BellBrook Thiazoles (WO2017176812A1)**: General methods described involve standard reactions like amide coupling, Suzuki coupling, reductions, and oxidations applied to thiazole-containing intermediates.[17]

### 10.2 Common Synthetic Strategies and Reactions

Across the different assignees and scaffolds, common synthetic strategies prevail:

- **Heterocycle Construction**: Various methods are used to build the core indole, quinoline, benzofuran, pyrimidine, and fused ring systems, often involving cyclization reactions (e.g., intramolecular Heck, condensation).
- **Coupling Reactions**: Palladium-catalyzed cross-couplings, particularly Suzuki coupling (for C-C bond formation, often attaching aryl/heteroaryl groups) and Sonogashira coupling (for C-C alkyne formation), are frequently employed.[13] Amide coupling reactions are ubiquitous for linking fragments or building side chains.[13] Ullmann coupling is also mentioned for C-N or C-O bond formation.[16]
- **Functional Group Interconversion**: Standard transformations like halogenation, esterification, hydrolysis, oxidation, reduction (using reagents like NaBH4, DIBAL-H, LAH), and protection/deprotection (especially Boc for amines, esters for acids) are routinely used.[13]
- **Chiral Synthesis/Separation**: For compounds with stereocenters (e.g., Roche's proline derivatives, ImmuneSensor's pyrrolidines), chiral starting

materials or separation techniques (chiral HPLC) are employed to obtain specific enantiomers or diastereomers.[18]

### 10.3 Potential Practicality and Scalability

The disclosed synthetic routes generally utilize well-established reactions common in medicinal chemistry. This suggests that, from a chemical feasibility standpoint, the synthesis of these inhibitors is practical on a laboratory scale.

However, scalability for manufacturing clinical or commercial quantities presents potential challenges:

- **Number of Steps**: Many routes involve multiple linear steps (often 5-10 or more), which can lead to lower overall yields and increased manufacturing complexity and cost.
- **Reagent Cost/Safety**: Some steps might employ expensive catalysts (e.g., Palladium, Iridium [16]) or hazardous reagents (e.g., BBr3 [13], strong bases, azide reagents [20]) that require careful handling and specialized equipment for large-scale synthesis.
- **Purification**: Multiple chromatographic purifications are often required in laboratory synthesis, which can be inefficient and costly on a large scale. Development of crystallization or alternative purification methods would be necessary.
- **Convergent Strategies**: Routes employing convergent strategies (synthesizing key fragments separately and coupling them late-stage) are generally preferred for scalability over long linear sequences. Some disclosed routes appear more linear than others.

Overall, while the chemistry is tractable, significant process development and optimization would be required to establish practical, cost-effective, and safe manufacturing routes for any clinical candidate progressing towards commercialization. The complexity of the multi-step syntheses underscores the significant investment required to produce these molecules.

## 11. Formulation and Physicochemical Properties

### 11.1 Claims and Examples Related to Salt Forms, Polymorphs, and Crystalline Forms

Patent applications for pharmaceutical compounds routinely include claims covering pharmaceutically acceptable salts, and often mention the possibility of solvates, hydrates, and polymorphs, even if specific forms are not yet characterized or selected.

- **Salts**: Patents from Novartis, Merck, Roche, ImmuneSensor, and BellBrook explicitly state that the invention includes pharmaceutically acceptable salts of the claimed cGAS inhibitors.[13] They often provide lists of suitable inorganic and organic acids (e.g., HCl, H2SO4, HBr, methanesulfonic acid, tartaric acid, fumaric acid) and bases (e.g., NaOH, KOH, organic amines) for salt formation. Specific examples synthesized or isolated as salts (e.g., HCl, TFA salts) are sometimes mentioned in the experimental sections.[13] The selection of an optimal salt form is critical for properties like solubility, stability, and manufacturability, and often occurs during later stages of preclinical development.
- **Polymorphs/Crystalline Forms**: The potential for polymorphism (existence of different crystalline forms) is acknowledged in some patents.[17] Different polymorphs can have distinct physical properties affecting dissolution rate, bioavailability, and stability. While the possibility is mentioned, detailed characterization or claims directed to specific polymorphs are generally absent in these relatively early-stage discovery patents. Identifying and controlling the desired crystalline form is a crucial aspect of pharmaceutical development.
- **Solvates/Hydrates**: Patents also typically cover solvated forms, including hydrates (where water is incorporated into the crystal lattice).[16] Like salts and polymorphs, the specific solvate form can influence stability and dissolution.

### 11.2 Disclosed Formulations and Excipients

The primary focus of the analyzed patents is the composition of matter of the cGAS inhibitors themselves. Detailed formulation information is usually limited. However, patents generally include standard boilerplate language describing the

possibility of formulating the compounds into various dosage forms (tablets, capsules, solutions, suspensions, injectables) using pharmaceutically acceptable carriers, diluents, and excipients.[13]

Given the target indications (chronic autoimmune/inflammatory diseases) and the explicit mention of oral candidates like IMSB-301 and VENT-03 [26], oral dosage forms (tablets, capsules) are the likely primary goal for many programs. Specific excipients are rarely detailed in these patents, but standard components like binders, fillers, disintegrants, lubricants, and coatings would be employed. For compounds with poor solubility, enabling formulations using techniques like amorphous solid dispersions, lipid-based formulations, or solubility enhancers (e.g., cyclodextrins like SBE-β-CD mentioned for formulating PF-06928215 in vitro/vivo [91]) might be necessary.

### 11.3 Disclosed Data on Physicochemical Properties

Concrete data on physicochemical properties like solubility, stability, permeability, and pharmacokinetics (PK) are sparsely disclosed in the analyzed patents.

- **Solubility**: Specific solubility data is rarely provided, although the need for formulation aids like DMSO, PEG300, Tween-80, or SBE-β-CD for *in vitro* or *in vivo* studies of some compounds (e.g., PF-06928215 [91], H-151 [94]) suggests that aqueous solubility might be a challenge for certain chemotypes. The development of prodrugs (e.g., Roche's esters [18]) also points towards efforts to overcome potential solubility or permeability limitations of the parent carboxylic acids.
- **Stability**: No specific stability data (e.g., chemical stability in solution, solid-state stability) was noted in the snippets. This is typically assessed during preclinical development.
- **Permeability**: Directly measured permeability data (e.g., Caco-2 assay) is not typically included in these patents. However, the frequent disconnect observed between biochemical potency and cellular activity for some early compounds [12] strongly suggests that poor cell permeability is a significant hurdle that medicinal chemistry programs must overcome. The successful

progression of oral candidates [26] implies that adequate permeability has been achieved for these molecules.

- **Pharmacokinetics (PK)**: Detailed PK data (absorption, distribution, metabolism, excretion - ADME) is generally absent from these discovery-stage patents. However, press releases or clinical trial information mention favorable PK profiles enabling once-daily dosing for clinical candidates like VENT-03 [38] and the assessment of PK in Phase 1 trials for IMSB-301.[26] Poor PK properties were noted as a limitation for some earlier STING inhibitors.[43]

In summary, while patents broadly cover formulation possibilities like salts, the specific forms and detailed physicochemical data crucial for drug development are often generated and potentially patented later. The emphasis on oral candidates highlights the importance of achieving good solubility, permeability, and PK properties, which remains a key challenge and differentiator in this field. The selection of a specific salt form, crystalline structure, and formulation for clinical development represents a critical downstream step with significant IP implications.

## 12. Geographic Analysis

### 12.1 Detailed Breakdown by Country/Region (US, EP, WO, CN, JP)

As established in Section 5.2, the patent landscape for small molecule cGAS inhibitors is global, with activity concentrated in the major pharmaceutical markets.

- **WO (PCT)**: Serves as the most common initial filing route, providing a basis for subsequent national/regional phase entries. A high percentage of patent families in this space likely have a WO publication.[13]
- **US**: Represents a primary jurisdiction for both filing and innovation origin. High levels of patenting activity are observed, reflecting the large market size and the significant presence of US-based pharmaceutical companies, biotechs, and academic institutions active in the field.[107] Many PCT applications enter the US national phase.[13]
- **EP**: The European Patent Office is another major target jurisdiction, with frequent regional phase entry from PCT applications.[13] This reflects the

importance of the European market.

- **CN**: China consistently appears as a designated state in PCT national phase entries for patents from various key players (Novartis, Merck, Roche, BellBrook, IFM).[13] This indicates a clear strategic interest in securing patent protection in the large and growing Chinese pharmaceutical market.
- **JP**: Similar to China, Japan is a frequent target for national phase entry, highlighting its status as a key Asian pharmaceutical market.[13]

### 12.2 Analysis of Filing Strategies

The predominant filing strategy observed is the use of the **Patent Cooperation Treaty (PCT)** system. Companies typically file an initial priority application (often in their home country, e.g., US or EP) followed by a PCT application within 12 months. This PCT application (published as a WO document) provides a unified international search and delays the significant costs associated with entering the national/regional phase in multiple individual countries or regions. Subsequently, applicants select key jurisdictions like the US, EP, CN, and JP for national/regional phase entry based on commercial interests and strategic priorities. This approach maximizes geographic coverage options while managing upfront costs. Direct filing into specific jurisdictions without an initial PCT application appears less common for globally active players in this field based on the analyzed data.

### 12.3 Regional Hot Spots for Innovation

Based on assignee headquarters and the origin of foundational research, the **United States** emerges as a major hot spot for innovation in small molecule cGAS inhibitors. This is driven by major pharmaceutical companies, numerous specialized biotechnology firms (like ImmuneSensor, Ventus, IFM, BellBrook), and leading academic institutions (like the University of Texas System).[13]

**Europe**, particularly Switzerland (home to Novartis and Roche) and potentially Germany and the UK (origins of related research or companies), also represents a significant center for R&D and patenting activity.[16]

While significant patent filings occur in **China** and **Japan**, indicating market importance, the data reviewed suggests that the primary innovation driving these

filings originates predominantly from US and European entities at present. However, given the rapid growth of the biomedical sector in China, it is plausible that domestic innovation in this area will increase in the future.[107]

### 13. Analysis of Key Patents/Patent Families

This section reviews selected patent families deemed significant based on their assignee, claimed chemical matter, potential relation to clinical candidates, or foundational nature. The focus remains on small molecule cGAS inhibitors within the 2015-present scope for US, EP, WO, CN, JP.

**Table 7: Analysis of Selected Key Patent Families**

| Patent Family ID (Exemplar) | Assignee(s) | Approx. Priority Date | Key Jurisdictions (Status Notes) | Core Scaffold Claimed | Key Claim Scope Summary | Disclosed Potency Range | Potential Impact/Notes |
|---|---|---|---|---|---|---|---|
| WO2014099824A1 / US10336786B2 [19] | University of Texas System | Dec 2012 | US (Granted), WO, EP, CA, CN, JP, etc. | N/A (Methods/Compositions) | Methods of modulating IFN response using cGAS/cGAMP; compo | N/A | Foundational IP covering the pathway components and modulation |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | sitions comprising cGAMP/analogues; screening methods. | | concepts. Potentially relevant for licensing/FTO for any cGAS modulator. |
| WO2017176812A1[17] | Immune Sensor LLC / UT System / BellBrook Labs? (Assignee varies/unclear across source | Apr 2016 | WO, US, EP, CN, JP, KR, AU (Pending/Granted varies) | Thiazole derivatives (Formula I) | Broad Markush claims covering substituted thiazole derivatives as cGAS antagonists. | Activity Categories A, B, C (IC50 ranges not defined) | Represents early industry effort on specific cGAS inhibitor scaffolds. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | s) | | | | | | |
| WO2019153002A1[21] | (Assignee unclear, linked to Ventus) | Feb 2018 | WO, US, EP, JP, BR, MX, IL (Pending/Status varies) | 1-(3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-2-hydroxyethanone derivatives | Claims specific pyrido[4,3-b]indole derivatives as cGAS inhibitors for autoimmune diseases. | Potent hcGAS inhibition claimed. | Covers scaffold relevant to Ventus' program (VENT-03). Potential FTO relevance. |
| WO2019201939A1[24] | EPFL (Ablasser Lab) | Apr 2018 | WO, EP (Withdrawn?) | Indole derivatives (H-151 analogues) | Primarily STING antagonists (covalent Cys91 binders), but releva | Potent STING inhibition. | Foundational work on covalent STING inhibitors (H-151), license |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | nt pathway IP. | | d/relevant to IFM/Novartis. |
| WO2020142735A1 [15] | BellBrook Labs | Jan 2019 | WO, US, EP, CN, JP, KR, AU, CA (Pending) | Pyrazole derivatives (Inferred) | Claims compounds/methods for inhibiting inappropriate IFN response via cGAS inhibition. | Not specified in snippet. | Further BellBrook Labs activity in the cGAS inhibitor space. |
| EP4267564A1 (WO2022137085A1) [16] | Novartis AG | Dec 2020 | EP, WO, US, CN, JP, AU, CA, KR, etc. (Pendi | Substituted 1H-Indole derivatives | Claims indole derivatives (e.g., C2-triazole, C3-pyrazo | Claims activity <= 30 µM; examples likely nM | Represents Novartis' specific chemical approa |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | ng) | | le) as cGAS inhibitors for autoimmune/inflammatory diseases. | range. | ch to cGAS inhibition. |
| AU2022273980A1 (WO2022238335A1) [18] | Roche / Genentech | May 2021 | AU, WO, EP, US, CN, JP, etc. (Pending) | Benzofuran-pyrimidine linked to Proline derivatives | Claims specific proline derivatives as potent and selective cellular cGAS inhibitors; includes prodrugs. | Low nM biochemical IC50; Sub-µM cellular IC50; Good selectivity. | Represents Roche's advanced chemical series with strong disclosed data. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| WO2023154962A1[13] | Merck & Co. | Feb 2022 | WO, EP, JP (Pending) | Pyrido[4,3-b]indoles, Benzofurans, Benzothiophenes, Indoles | Claims diverse scaffolds as cGAS inhibitors for autoimmune and neurodegenerative diseases. | Activity categories (+, ++, +++) reported. | Shows Merck's broad exploration of chemical space for cGAS inhibitors. Overlaps with Ventuson pyridoindole scaffold. |
| US12091387B2 (related to WO2023150 | ImmuneSensor Therapeutics / UT Syste | Mar 2022 | US (Granted), WO, EP, AU, CA, | Quinoline derivatives | Claims specific quinoline derivatives | Not specified in snippet, but likely covers | Covers clinical candidate IMSB-301 scaffol |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 823A1) [20] | m | | CN, JP, etc. (Pending/Granted varies) | | (e.g., C7/C8 halo, C4 triazole, C2 pyrrolidine-linker-acid) as cGAS antagonists. | IMSB-301. | d. Highly relevant for FTO. |

**Detailed Review Insights:**

- **Foundational IP (UT System)**: Patents like US10336786B2 [28] stemming from the original discovery work cover fundamental aspects of the pathway and its modulation. While potentially broad, their direct impact on specific small molecule inhibitors developed later requires careful claim construction, but they establish the initial landscape and licensing basis.
- **Scaffold-Specific Patents (Industry)**: Subsequent patents from industry players (Novartis, Merck, Roche, ImmuneSensor, Ventus, BellBrook) focus on specific chemical scaffolds. These patents typically include broad Markush claims covering analogues and specific claims to exemplified compounds.
  - *Novartis (Indoles)* [16]: Claims focus on substituted indoles with specific heterocyclic groups at C2 and C3. The breadth suggests exploration around this core.
  - *Roche (Proline-linked Benzofuran-pyrimidines)* [18]: Claims a very specific chemotype with detailed SAR and cellular data, including prodrugs. The high potency and selectivity reported make this family significant.

- *Merck (Diverse Scaffolds)* [13]: Claims cover multiple distinct scaffolds, indicating a wide-ranging discovery effort. The inclusion of pyrido[4,3-b]indoles creates potential overlap with Ventus. The focus on neurodegenerative indications is also notable.
- *ImmuneSensor (Quinolines)* [20]: Claims focus on substituted quinolines, likely covering their clinical candidate IMSB-301. The granted US patent provides strong protection in a key market for this specific chemical space.
- *Ventus (Pyridoindoles)* [21]: Claims focus on pyrido[4,3-b]indole derivatives, overlapping with Merck's filings but potentially covering their specific clinical candidate VENT-03.

- **Clinical Candidate Coverage**: Patents covering structures related to clinical candidates (IMSB-301, VENT-03) are particularly impactful. Their claims define the proprietary space around these advanced assets and are critical for FTO assessments for competitors working on similar scaffolds.
- **Claim Scope Evolution**: It is probable that the granted claims for some of these families are narrower than the initial broad claims filed in WO or initial national applications, due to prosecution history and prior art considerations. Assessing the granted claims in key jurisdictions (especially US, EP) is essential for accurate FTO analysis. The evolution from broad foundational patents to narrower, optimized compound patents is evident.



## 14. Freedom-to-Operate (FTO) Considerations

Assessing FTO in the small molecule cGAS inhibitor space requires careful consideration of the complex patent landscape outlined in previous sections. This analysis is based on the publicly available information within the training data and does not constitute a formal legal opinion; a dedicated FTO analysis by patent professionals using live databases is necessary for definitive conclusions.

### 14.1 Potential FTO Risks

Several factors contribute to potential FTO risks for new entrants or existing players developing cGAS inhibitors:

- **Foundational Patents**: Early patents from academic institutions like the University of Texas System, covering the cGAS enzyme, cGAMP, and general

methods of pathway modulation, might possess broad claims that could be asserted against downstream product developers.[19] The scope and validity of these claims concerning specific small molecule inhibitors developed years later would need careful evaluation, but they represent a potential licensing requirement or litigation risk.

- **Crowded Chemical Scaffolds**: Certain chemical scaffolds appear to be pursued by multiple competitors. The **pyrido[4,3-b]indole** core, for instance, features in patents assigned to both Merck and Ventus Therapeutics.[13] Developing new inhibitors based on this scaffold would necessitate meticulous analysis of the claims in patents from both entities to ensure freedom to operate. Similarly, the general **indole** space sees activity from Novartis and Merck.[13] Operating in these crowded areas increases the risk of infringing existing composition of matter claims.
- **Broad Markush Claims**: Early industry patents often contain broad Markush claims covering numerous potential analogues around a core scaffold.[13] Even if a specific new compound is not explicitly exemplified, it might still fall within the scope of a competitor's broad Markush claim, posing an FTO risk. The enforceability of such broad claims can vary by jurisdiction and depends on factors like enablement and written description support.
- **Patents Covering Clinical Candidates**: Patents protecting the specific structures or close analogues of clinical candidates like ImmuneSensor's IMSB-301 (likely quinolines claimed in US12091387B2 [20]) or Ventus' VENT-03 (likely pyridoindoles claimed in WO2019153002A1 family [21]) represent significant FTO hurdles for others working on similar molecules. These patents are likely to be vigorously defended.
- **Method of Use Claims**: While composition of matter claims provide the strongest protection, broad method of use claims targeting specific diseases (e.g., "treating SLE with a cGAS inhibitor") could also pose risks, although they are generally considered easier to design around or challenge.

### 14.2 Potential Blocking Patents

Based on the analysis, the following patent families (represented by exemplar documents) warrant close FTO scrutiny:

- **UT System Foundational Patents (e.g., US10336786B2)**: Potential broad relevance to any cGAS modulation strategy.
- **ImmuneSensor Quinoline Patents (e.g., US12091387B2)**: Likely cover IMSB-301 and related analogues; critical for competitors in the quinoline space.
- **Ventus Pyridoindole Patents (e.g., WO2019153002A1)**: Likely cover VENT-03 and related analogues; critical for competitors in this scaffold space.
- **Merck Pyridoindole/Diverse Scaffold Patents (e.g., WO2023154962A1)**: Broad claims across multiple scaffolds, including overlap with Ventus; requires careful analysis depending on the competitor's structure.
- **Roche Proline-linked Benzofuran-pyrimidine Patents (e.g., AU2022273980A1)**: Cover a distinct, potent chemical series; potentially blocking for similar structures.
- **Novartis Indole Patents (e.g., EP4267564A1)**: Cover specific indole-based inhibitors; relevant for competitors exploring similar indole chemistry.

The specific claims (particularly granted claims in relevant jurisdictions like US and EP) of these and other relevant patents must be analyzed in detail against any proposed new chemical entity.

### 14.3 Potential FTO Opportunities

Despite the risks, potential FTO opportunities might exist:

- **Novel Chemical Space**: Developing inhibitors based on genuinely novel scaffolds not covered by existing claims represents the clearest FTO path, although discovering such scaffolds with desirable properties is challenging.
- **Alternative Mechanisms**: Focusing on mechanisms other than direct active site competition (e.g., allosteric inhibition, disrupting DNA binding or dimerization) might circumvent existing composition of matter claims focused on active site binders, provided the compounds themselves are structurally distinct.
- **Geographic Limitations**: Some patents may not be filed or granted in all desired commercial jurisdictions (though key players appear to file broadly in US/EP/WO/CN/JP). A thorough geographic FTO search could reveal specific regional opportunities.

- **Narrowed Claim Scope**: Granted claims are often narrower than initially filed claims. Careful analysis of the prosecution history and final granted claims of potentially blocking patents might reveal scope limitations that allow for design-arounds.
- **Licensing**: Obtaining licenses for foundational IP (e.g., from universities) or potentially blocking patents from competitors (if feasible) can provide FTO.
- **Patent Expiry**: While most specific cGAS inhibitor patents are recent (post-2015) and far from expiry, some very early foundational patents related to the pathway might eventually expire, although their direct impact on specific later compounds is often debatable.

Navigating the FTO landscape requires a multi-layered approach, considering foundational IP, broad scaffold patents, and specific competitor compound patents. For later entrants, demonstrating significant, non-obvious improvements over existing art or focusing on truly novel chemical or mechanistic space will be crucial for securing patent protection and FTO.

## 15. Future Trends and Outlook

### 15.1 Predicted Patenting Activity and Trends

Patenting activity in the small molecule cGAS inhibitor field is expected to remain robust in the near term, driven by ongoing clinical development and continued interest in the therapeutic potential of modulating this pathway. Key trends likely include:

- **Focus on Optimization**: A significant portion of future filings will likely focus on optimizing existing chemical scaffolds (indoles, quinolines, pyridoindoles, benzofuran-pyrimidines, etc.). This will involve fine-tuning substituents to improve potency, selectivity (over STING and other targets), pharmacokinetic properties (especially oral bioavailability, half-life, CNS penetration where desired), and safety profiles. Patents may claim specific optimized compounds, salts, polymorphs, or formulations designed for clinical success.
- **Second-Generation Inhibitors**: Efforts will likely intensify to discover "second-generation" inhibitors that overcome limitations of earlier compounds (e.g., poor cellular activity, species selectivity issues). This may involve exploring

subtle modifications of known scaffolds or entirely new chemical matter.

- **Novel Mechanisms**: While active site inhibition dominates, expect increased exploration and patenting of inhibitors targeting alternative mechanisms, such as allosteric sites, disruption of cGAS dimerization, or blocking DNA binding.[7] Covalent inhibitors [34] and potentially targeted degradation approaches (e.g., PROTACs [42]) may also see increased patent activity as alternative strategies.
- **Combination Therapies**: As monotherapies advance, patents covering combination therapies (e.g., a cGAS inhibitor combined with other immunosuppressive or anti-inflammatory agents for autoimmune diseases) may emerge.
- **Expanding Indications**: Filings may increasingly claim or provide data supporting utility in a broader range of indications beyond core autoimmune diseases, including fibrosis, neurodegenerative disorders [13], and potentially aging-related conditions.[13]

### 15.2 Identification of White Spaces for Future Innovation

Based on the current landscape, areas for future innovation and potential white space include:

- **Structurally Novel Scaffolds**: Discovering and patenting truly novel chemical scaffolds distinct from the currently prevalent heterocyclic systems remains a significant opportunity, although challenging.
- **Targeting Non-Canonical Functions**: Exploring inhibitors that selectively modulate specific cGAS functions (e.g., its role in DNA repair or senescence [3]) beyond just cGAMP synthesis could open new therapeutic avenues and IP space.
- **CNS-Penetrant Inhibitors**: Developing potent, selective, and orally bioavailable inhibitors capable of crossing the blood-brain barrier is a key need for treating neuroinflammatory and neurodegenerative conditions linked to cGAS activation.[13] This property space appears less explored currently.
- **Targeted Delivery**: Strategies for targeted delivery of cGAS inhibitors to

specific tissues or cell types (e.g., inflamed tissues, specific immune cells) could enhance efficacy and reduce potential systemic side effects, representing an area for formulation or conjugation-based IP. (Analogy: STING agonist ADCs [81]).

- **Underserved Indications**: Focusing R&D and patenting efforts on specific autoimmune or inflammatory conditions where cGAS plays a role but which are less frequently cited in current patents compared to SLE or AGS.

### 15.3 Emerging Chemical Scaffolds or Approaches

Recent patents and publications hint at emerging trends:

- **Covalent Inhibition**: While most inhibitors appear non-covalent, the development of covalent STING inhibitors (targeting Cys91) [34] raises the possibility of exploring covalent strategies for cGAS, targeting specific residues.
- **Peptide/Macrocycle Inhibitors**: The discovery of cyclopeptide inhibitors targeting the cGAS DNA binding site [35] suggests that modalities beyond traditional small molecules might be viable.
- **Targeted Degradation (PROTACs)**: The concept of using PROTACs to degrade target proteins is gaining traction in drug discovery. While current examples target downstream proteins like CRBN [42], developing cGAS-specific PROTACs could be a future direction.
- **Focus on Species Cross-Reactivity**: The explicit effort by Roche to engineer inhibitors with dual human/mouse potency [14] highlights the recognition of species selectivity as a key challenge and suggests future efforts may prioritize compounds active across relevant preclinical species.

The outlook for small molecule cGAS inhibitors is promising, driven by strong biological rationale and advancing clinical candidates. Future success will likely hinge on developing differentiated molecules with superior drug-like properties, navigating the competitive IP landscape, and demonstrating clear clinical benefit in targeted patient populations. The field is poised for continued innovation, potentially expanding beyond traditional active site inhibition and core autoimmune indications.

## 16. Conclusion

This patent landscape review provides a detailed analysis of the intellectual property and competitive environment surrounding small molecule inhibitors of cGAS, focusing on developments from 2015 to the present across key global jurisdictions (US, EP, WO, CN, JP) and relevant to autoimmune and inflammatory diseases.

The analysis confirms that cGAS inhibition has emerged as a highly active and competitive field in therapeutic research. Driven by the understanding that aberrant cGAS-STING pathway activation underlies numerous debilitating conditions characterized by excessive type I interferon signaling and inflammation [4], significant R&D investment has fueled a surge in patent filings since 2015. Key players include a mix of global pharmaceutical companies (Novartis, Merck, Roche), specialized biotechs (ImmuneSensor, Ventus, IFM Due (now Novartis), BellBrook Labs), and foundational academic institutions (University of Texas System).

The chemical space explored is diverse, dominated by heterocyclic scaffolds such as indoles, quinolines, pyridoindoles, and benzofuran derivatives, primarily designed to target the cGAS enzymatic active site.[13] The rapid progression of orally available candidates like IMSB-301 and VENT-03 into clinical trials signifies the field's dynamism and the strategic focus on developing convenient therapies for chronic diseases.[26]

Despite the progress, challenges remain. Translating potent biochemical inhibition into effective cellular activity and achieving desirable pharmacokinetic profiles for oral administration are key hurdles.[18] Species-specific differences in cGAS structure can complicate preclinical validation.[14] Furthermore, the patent landscape is becoming increasingly crowded, particularly around certain chemical scaffolds, presenting potential FTO complexities.[13]

Future directions will likely involve the development of second-generation inhibitors with optimized properties, exploration of novel chemical matter and alternative inhibitory mechanisms (allosteric, covalent, DNA-binding site), and

investigation of therapeutic potential in a broader range of indications, including neuroinflammation and fibrosis.[13]

In conclusion, the small molecule cGAS inhibitor landscape is vibrant and holds considerable therapeutic promise. However, it is also characterized by intense competition and significant IP challenges. Success for current and future players will depend on scientific innovation leading to differentiated clinical candidates, strategic navigation of the patent environment, and ultimately, demonstration of safety and efficacy in treating diseases driven by aberrant cGAS activity.

## 17. Appendices

**(Note: Content for tables is summarized from the main report sections)**

### A. List of Key Patent Families Analyzed for Small Molecule cGAS Inhibitors

*(See Table 7 in Section 13 for details)*

- WO2014099824A1 / US10336786B2 (University of Texas System) - Foundational Pathway IP
- WO2017176812A1 (Immune Sensor LLC / UT System / BellBrook Labs?) - Thiazole Derivatives
- WO2019153002A1 (Ventus Therapeutics related) - Pyrido[4,3-b]indole Derivatives
- WO2019201939A1 (EPFL - Ablasser Lab) - Indole Derivatives (STING Antagonists)
- WO2020142735A1 (BellBrook Labs) - Pyrazole Derivatives
- EP4267564A1 / WO2022137085A1 (Novartis AG) - Substituted 1H-Indole Derivatives
- AU2022273980A1 / WO2022238335A1 (Roche / Genentech) - Benzofuran-pyrimidine-Proline Derivatives
- WO2023154962A1 (Merck & Co.) - Diverse Scaffolds (Pyridoindoles, Benzofurans, etc.)
- US12091387B2 / WO2023150823A1 (ImmuneSensor Therapeutics / UT System) - Quinoline Derivatives

**B. Summary Tables of Raw Search Results or Data**

Table 1: Estimated Patent Filing Trend (Small Molecule cGAS Inhibitors, 2015-Present)
(As presented in Section 5.1)
Table 2: Estimated Geographic Distribution Summary (Small Molecule cGAS Inhibitors, 2015-Present)
(As presented in Section 5.2)
Table 3: Key Assignees in Small Molecule cGAS Inhibition (2015-Present)
(As presented in Section 6)

**C. Descriptions of Charts and Graphs Visualizing Key Findings**

*(Descriptions of potential visualizations, not generated by AI)*

- **Figure 1: Patent Filing Trend (2015-Present)**: A bar chart showing the estimated number of new patent families published or prioritized per year from 2015 onwards, illustrating the growth and potential peak in filing activity.
- **Figure 2: Geographic Distribution of Filings**: A pie chart or bar chart showing the percentage distribution of patent family filings across the key jurisdictions (US, EP, WO, CN, JP).
- **Figure 3: Top Assignee Activity**: A bar chart comparing the estimated number of relevant patent families for the key assignees identified in Table 3.
- **Figure 4: Chemical Space Map (Conceptual)**: A 2D scatter plot conceptually representing the chemical space of claimed inhibitors based on calculated properties or fingerprints, potentially highlighting clusters associated with different scaffolds or assignees and identifying less populated areas (white space).

**D. Representative Key Chemical Structures of cGAS Inhibitors Identified**

Table 4: Representative Claimed Chemical Structures for cGAS Inhibition
(As presented in Section 8.3)

**E. Summary Tables of Available Structure-Activity Relationship (SAR) Data**

Table 5: Summary of Representative Disclosed SAR Data for cGAS Inhibitors
(As presented in Section 9.1)

**F. Summaries of Representative Disclosed Synthetic Routes**

(Textual summary based on Section 10)

Synthetic routes generally involve multi-step sequences using standard organic reactions like Suzuki coupling, amide coupling, Sonogashira coupling, heterocycle formation (e.g., indole synthesis via cycloisomerization or Heck coupling, quinoline synthesis, triazole formation), and functional group interconversions (halogenation, reduction, oxidation, protection/deprotection). Key intermediates often include functionalized heterocyclic building blocks (e.g., substituted indoles, quinolines, benzofurans, pyrimidines, pyrrolidines, pyridines, triazoles, pyrazoles) and boronic acids/esters or halides for coupling reactions. Specific examples include Novartis' indole synthesis 16, Merck's routes to pyridoindoles and benzofurans 13, Roche's synthesis of proline-linked benzofuran-pyrimidines 18, and ImmuneSensor's quinoline synthesis.20

**G. Summaries of Relevant Physicochemical Data or Formulation Details**

Table 6: Summary of Disclosed Formulation/Physicochemical Data
(Content summarized from Section 11)

| **Assignee/Patent** | **Compound/ Scaffold** | **Mentioned Salt Forms** | **Mentioned Formulations** | **Disclosed Properties (Solubility, Stability, PK Notes)** |
|---|---|---|---|---|
| General [16] | Various Inhibitors | Pharmaceutically acceptable salts (acid/base | Standard oral (tablet, capsule) and injectable forms | Limited data in early patents. |

| | | | | |
|---|---|---|---|---|
| | | addition) broadly claimed/discussed. Specific examples: HCl, TFA. | mentioned. Standard excipients discussed. | |
| Pfizer [91] | PF-06928215 | Not specified | Requires DMSO/PEG/ Tween or SBE-β-CD for solubilization in assays. | Poor cellular activity suggests permeability issues. |
| Roche [18] | Benzofuran-pyrimidine-proline | Pharmaceutically acceptable salts claimed. | Methyl ester prodrugs discussed. | Prodrugs show reduced biochemical but retained cellular activity. |
| ImmuneSensor [26] | IMSB-301 (Quinoline) | Not specified | Oral formulation (Phase 1). | PK assessed in Phase 1. |
| Ventus [38] | VENT-03 (Pyridoindole) | Not specified | Oral formulation (Phase 1). | Favorable PK for once-daily dosing reported |

| | | | | |
|---|---|---|---|---|
| | | | | from Phase 1. |
| InvivoGen [94] | H-151 (STING Inhibitor) | Not specified | Soluble in DMSO (20 mg/mL). | Used in cell culture and *in vivo* mouse models. |

**18. Formatting Guidelines (for Word Document)**

*(Acknowledgement: The structure and content of this report adhere to the requested outline and formatting principles. LaTeX was used conceptually for mathematical notation where applicable. If exported, standard Word formatting guidelines including Font (Arial/Times New Roman, 12pt), Headings (Word Styles H1, H2, etc.), Line Spacing (1.5 lines), Margins (1 inch), Paragraphs (single blank line, no indent), Lists (standard bullets/numbers), Tables/Figures (numbered, titled/captioned), Page Numbering (footer right), and Table of Contents (automatic) should be applied.)*



**Works cited**


1. The role of cGAS-STING pathway ubiquitination in innate immunity and multiple diseases - Frontiers, accessed April 30, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2025.1522200/full
2. Control of innate immunity by the cGAS-STING pathway - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/35485309/
3. Biochemistry, Cell Biology, and Pathophysiology of the Innate ..., accessed April 30, 2025, https://www.annualreviews.org/doi/10.1146/annurev-biochem-040320-101629
4. multifaceted functions of cGAS | Journal of Molecular Cell Biology - Oxford Academic, accessed April 30, 2025, https://academic.oup.com/jmcb/article/14/5/mjac031/6583286
5. Updated roles of cGAS-STING signaling in autoimmune diseases ..., accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10538533/

6. Emerging role of the cGAS-STING signaling pathway in autoimmune diseases: Biologic function, mechanisms and clinical prospection - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/35902046/
7. Inhibitory targeting cGAS-STING-TBK1 axis: Emerging strategies for autoimmune diseases therapy - Frontiers, accessed April 30, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.954129/full
8. The cGAS-STING pathway as a therapeutic target in inflammatory ..., accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/33833439/
9. Medicinal chemistry perspective on cGAS-STING signaling pathway with small molecule inhibitors - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/363837827_Medicinal_chemistry_perspective_on_cGAS-STING_signaling_pathway_with_small_molecule_inhibitors
10. cGAS - The long awaited cytosolic DNA sensor | Review - InvivoGen, accessed April 30, 2025, https://www.invivogen.com/review-cgamp
11. Development of human cGAS-specific small-molecule inhibitors for repression of dsDNA-triggered interferon expression, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6529454/
12. Development of human cGAS-specific small-molecule inhibitors for repression of dsDNA-triggered interferon expression, accessed April 30, 2025, https://www.regenhealthsolutions.info/wp-content/uploads/2019/06/Development-of-human-cGAS-specific-smallmolecule-inhibitors-for-repression-of-dsDNAtriggered-interferon-expression.pdf
13. WO2023154962A1 - Cgas inhibitors and uses thereof - Google ..., accessed April 30, 2025, https://patents.google.com/patent/WO2023154962A1/en
14. Structural insight into the cGAS active site explains differences between therapeutically relevant species - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/390095544_Structural_insight_into_the_cGAS_active_site_explains_differences_between_therapeutically_relevant_species
15. WO2020142735A1 - Inhibitors of cgas activity as therapeutic agents - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/WO2020142735A1/en
16. EP4267564A1 - Indole derivatives useful in treating conditions ..., accessed April 30, 2025, https://patents.google.com/patent/EP4267564A1/en

17. WO2017176812A1 - cGAS ANTAGONIST COMPOUNDS - Google ..., accessed April 30, 2025, https://patents.google.com/patent/WO2017176812A1/en
18. patentimages.storage.googleapis.com, accessed April 30, 2025, https://patentimages.storage.googleapis.com/07/d9/01/b2d670c5b59d05/AU2022273980A1.pdf
19. WO2014099824A1 - Pharmaceutical targeting of a mammalian cyclic di-nucleotide signaling pathway - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/WO2014099824A1/und
20. US12091387B2 - Quinoline cGAS antagonist compounds - Google ..., accessed April 30, 2025, https://patents.google.com/patent/US12091387B2/en
21. WO2019153002A1 - 2,3,4,5-tetrahydro-1h-pyrido[4, 3-b]indole inhibitors of cgas for treating autoinflammatory diseases - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/WO2019153002A1/en
22. JP2022531755A - CGAS inhibitors for the treatment of autoinflammatory diseases and cancer metastases - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/JP2022531755A/en
23. EP3439667A4 - CGAS ANTAGONIST COMPOUNDS - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/EP3439667A4/en
24. WO2019201939A1 - Sting inhibitors - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/WO2019201939A1/en
25. New Review Examines the cGAS–STING Pathway as a Therapeutic Target in Inflammatory Diseases, accessed April 30, 2025, https://www.ifmthera.com/news/new-review-examines-the-cgas-sting-pathway-as-a-therapeutic-target-in-inflammatory-diseases/
26. ImmuneSensor Therapeutics Granted New U.S. Patent for its Oral cGAS Inhibitors, accessed April 30, 2025, https://www.globenewswire.com/news-release/2024/09/17/2947387/0/en/ImmuneSensor-Therapeutics-Granted-New-U-S-Patent-for-its-Oral-cGAS-Inhibitors.html
27. cGAS INHIBITORS - Justia Patents, accessed April 30, 2025, https://patents.justia.com/patent/20240246979
28. US10336786B2 - Pharmaceutical targeting of a mammalian cyclic di-nucleotide signaling pathway - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/US10336786B2/und
29. Ventus therapeutics u s incPatents | PatentGuru, accessed April 30, 2025, https://www.patentguru.com/assignee/ventus-therapeutics-u-s-inc
30. IFM Cinque, Inc. - Drug pipelines, Patents, Clinical trials - Patsnap Synapse,

accessed April 30, 2025, https://synapse.patsnap.com/organization/6de11a66a5c302307b0bb4e78f96d8aa
31. Targeting Stimulator of Interferon Genes (STING): A Medicinal Chemistry Perspective | Request PDF - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/337882378_Targeting_Stimulator_of_Interferon_Genes_STING_A_Medicinal_Chemistry_Perspective
32. Design, Synthesis, and Biological Evaluation of Selective STING Synergists That Enhance cGAMP-STING Pathway Activation without Inherent Agonist Activity | Journal of Medicinal Chemistry - ACS Publications, accessed April 30, 2025, https://pubs.acs.org/doi/10.1021/acs.jmedchem.4c03131
33. Discovery of MK-1454: A Potent Cyclic Dinucleotide Stimulator of Interferon Genes Agonist for the Treatment of Cancer | Journal of Medicinal Chemistry - ACS Publications, accessed April 30, 2025, https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.1c02197
34. Orally Bioavailable and Site-Selective Covalent STING Inhibitor Derived from a Macrocyclic Marine Diterpenoid | Journal of Medicinal Chemistry - ACS Publications, accessed April 30, 2025, https://pubs.acs.org/doi/10.1021/acs.jmedchem.4c02665
35. Discovery of Small Molecule Cyclic GMP-AMP Synthase Inhibitors - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/337925116_Discovery_of_Small_Molecule_Cyclic_GMP-AMP_Synthase_Inhibitors
36. ImmuneSensor Therapeutics Initiates Phase 1 Trial of IMSB301, a Leading cGAS Inhibitor, accessed April 30, 2025, https://synapse-patsnap-com.libproxy1.nus.edu.sg/blog/immunesensor-therapeutics-initiates-phase-1-trial-of-imsb301-a-leading-cgas-inhibitor
37. IMSB-301 - Drug Targets, Indications, Patents - Patsnap Synapse, accessed April 30, 2025, https://synapse.patsnap.com/drug/ff8b7339f85a4b679ff485130d446f64
38. Ventus Therapeutics - Products, Competitors, Financials, Employees, Headquarters Locations - CB Insights, accessed April 30, 2025, https://www.cbinsights.com/company/ventus-therapeutics
39. VENT-03 - Drug Targets, Indications, Patents - Patsnap Synapse, accessed April 30, 2025, https://synapse.patsnap.com/drug/98392000f7404814935800b1d04f7a3e
40. Leveraging the cGAS-STING Pathway - ImmuneSensor Therapeutics,

accessed April 30, 2025, https://www.immunesensor.com/science/cgas-sting-pathway/
41. Ventus Therapeutics Announces Publication in Nature's Communications Chemistry Describing the Structure-based Optimization of a New Series of cGAS Inhibitors - BioSpace, accessed April 30, 2025, https://www.biospace.com/press-releases/ventus-therapeutics-announces-publication-in-natures-communications-chemistry-describing-the-structure-based-optimization-of-a-new-series-of-cgas-inhibitors
42. PF-06928215 is a high affinity cGAS inhibitor. (A)... | Download Scientific Diagram - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/figure/PF-06928215-is-a-high-affinity-cGAS-inhibitor-A-Concentration-dependent-inhibition-in_fig5_319974257
43. Potential Therapeutic Value of the STING Inhibitors - MDPI, accessed April 30, 2025, https://www.mdpi.com/1420-3049/28/7/3127
44. A/Prof Seth Masters Qualification: PhD Institution: WEHI Date: 12/11/20 Title of Project: Blocking neuroinflammation to treat ALS Summary - Brain Foundation, accessed April 30, 2025, https://brainfoundation.org.au/wp-content/uploads/2019/10/Masters-Seth-Neuroinflammation-in-ALS-1.pdf
45. Orally Bioavailable and Site-Selective Covalent STING Inhibitor Derived from a Macrocyclic Marine Diterpenoid - PMC, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11912488/
46. Orally Bioavailable and Site-Selective Covalent STING Inhibitor Derived from a Macrocyclic Marine Diterpenoid | Request PDF - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/389399869_Orally_Bioavailable_and_Site-Selective_Covalent_STING_Inhibitor_Derived_from_a_Macrocyclic_Marine_Diterpenoid
47. cGAS: action in the nucleus - Frontiers, accessed April 30, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1380517/full
48. Updated roles of cGAS-STING signaling in autoimmune diseases - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/37781360/
49. The role of the cGAS-STING signaling pathway in viral infections, inflammatory and autoimmune diseases - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/38822084/
50. CGAS in Innate Immunity | Encyclopedia MDPI, accessed April 30, 2025,

https://encyclopedia.pub/entry/6492
51. The role of cGAS-STING pathway ubiquitination in innate immunity and multiple diseases, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/40028324/
52. Significance of the cGAS-STING Pathway in Health and Disease - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/37686127/
53. Regulation and function of the cGAS-STING pathway: Mechanisms, post-tr | DDDT, accessed April 30, 2025, https://www.dovepress.com/regulation-and-function-of-the-cgas-sting-pathway-mechanisms-post-tran-peer-reviewed-fulltext-article-DDDT
54. Therapeutic Development by Targeting the cGAS-STING Pathway in Autoimmune Disease and Cancer - Frontiers, accessed April 30, 2025, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.779425/full
55. Intervention of cGAS–STING signaling in sterile inflammatory diseases - Oxford Academic, accessed April 30, 2025, https://academic.oup.com/jmcb/article/14/2/mjac005/6515952
56. Targeting STING oligomerization with small-molecule inhibitors - PNAS, accessed April 30, 2025, https://www.pnas.org/doi/10.1073/pnas.2305420120
57. The Cytosolic DNA-Sensing cGAS–STING Pathway in Cancer - AACR Journals, accessed April 30, 2025, https://aacrjournals.org/cancerdiscovery/article/10/1/26/2314/The-Cytosolic-DNA-Sensing-cGAS-STING-Pathway-in
58. Small molecule inhibition of human cGAS reduces total cGAMP output and cytokine expression in cells, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7200739/
59. Full article: Protein-protein interactions in cGAS-STING pathway: a medicinal chemistry perspective - Taylor & Francis Online, accessed April 30, 2025, https://www.tandfonline.com/doi/full/10.1080/17568919.2024.2383164?src=
60. Discovery of Potent and Orally Bioavailable Pyrimidine Amide cGAS Inhibitors via Structure-Guided Hybridization | CoLab, accessed April 30, 2025, https://colab.ws/articles/10.1021/acsmedchemlett.4c00471
61. www.frontiersin.org, accessed April 30, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1380517/full#:~:text=In%20fact%2C%20cGAS%20plays%20the,derived

%20dendritic%20cells%20(DCs).
62. (PDF) The role of cGAS-STING pathway ubiquitination in innate immunity and multiple diseases - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/389404128_The_role_of_cGAS-STING_pathway_ubiquitination_in_innate_immunity_and_multiple_diseases
63. Role of Post-Translational Modifications of cGAS in Innate Immunity - MDPI, accessed April 30, 2025, https://www.mdpi.com/1422-0067/21/21/7842
64. Small molecule innate immune modulators in cancer therapy - Frontiers, accessed April 30, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1395655/pdf
65. Design, Synthesis, and Biochemical and Biological Evaluation of Novel 7-Deazapurine Cyclic Dinucleotide Analogues as STING Receptor Agonists, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9620234/
66. Small molecules targeting the innate immune cGAS–STING–TBK1 signaling pathway - PMC - PubMed Central, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7745059/
67. Orally bioavailable STING antagonist synthesized via multi-component Povarov–Doebner type reaction - RSC Publishing Home, accessed April 30, 2025, https://pubs.rsc.org/en/content/articlehtml/2024/cc/d4cc03228d
68. Agonists and Inhibitors of the cGAS-STING Pathway - MDPI, accessed April 30, 2025, https://www.mdpi.com/1420-3049/29/13/3121
69. Discovery and optimization of narrow spectrum inhibitors of Tousled like kinase 2 (TLK2) using quantitative structure activity r - ePrints Soton - University of Southampton, accessed April 30, 2025, https://eprints.soton.ac.uk/491136/1/1-s2.0-S022352342400237X-main.pdf
70. Progress of cGAS-STING signaling pathway-based modulation of immune response by traditional Chinese medicine in clinical diseases - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/39737190/
71. IUPHAR ECR review: The cGAS-STING pathway: Novel functions beyond innate immune and emerging therapeutic opportunities - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/38216006/
72. The role of the cGAS-STING pathway in chronic pulmonary inflammatory diseases - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/39540037/
73. Emerging Roles of cGAS-STING Signaling in Mediating Ocular Inflammation -

PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/37778330/
74. The cGAS–STING pathway as a therapeutic target in inflammatory diseases - PMC, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC8029610/
75. Intervention of cGAS–STING signaling in sterile inflammatory diseases - PMC, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9122663/
76. The cGAS-STING pathway in cancer immunity: dual roles, therapeutic strategies, and clinical challenges - Portland Press, accessed April 30, 2025, https://portlandpress.com/essaysbiochem/article/doi/10.1042/EBC20253006/235810/The-cGAS-STING-pathway-in-cancer-immunity-dual
77. A small-molecule inhibitor and degrader of the RNF5 ubiquitin ligase, accessed April 30, 2025, https://www.molbiolcell.org/doi/10.1091/mbc.E22-06-0233
78. Structure–Activity Relationship Study of 1H-Pyrrole-3-carbonitrile Derivatives as STING Receptor Agonists - PMC, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10424313/
79. A kinase-cGAS cascade to synthesize a therapeutic STING activator - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/publication/359270808_A_kinase-cGAS_cascade_to_synthesize_a_therapeutic_STING_activator
80. Novel emerging nano-assisted anti-cancer strategies based on the STING pathway - ScienceOpen, accessed April 30, 2025, https://www.scienceopen.com/hosted-document?doi=10.15212/AMM-2023-0023
81. Tumor-targeted delivery of a STING agonist improves cancer immunotherapy - PNAS, accessed April 30, 2025, https://www.pnas.org/doi/abs/10.1073/pnas.2214278119
82. Recent advances in the development of STING inhibitors: an updated patent review - informa Healthcare, accessed April 30, 2025, https://www.informahealthcare.com/doi/epub/10.1080/13543776.2022.2144220
83. The cGAS/STING Pathway—A New Potential Biotherapeutic Target for Gastric Cancer?, accessed April 30, 2025, https://www.mdpi.com/2075-4426/14/7/736
84. Biological and therapeutic significance of targeting NLRP3 inflammasome in

the brain and the current efforts to develop brain-penetrant inhibitors - PMC - PubMed Central, accessed April 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11955958/
85. Targeting the NLRP3 Inflammasome: Novel Inhibitors for Cardiovascular Disease Management - Preprints.org, accessed April 30, 2025, https://www.preprints.org/manuscript/202501.1297/v1/download
86. Top 1277 Journal of Medicinal Chemistry papers published in 2024 - SciSpace, accessed April 30, 2025, https://scispace.com/journals/journal-of-medicinal-chemistry-1vm1ozsh/2024
87. Target-Based Evaluation of "Drug-Like" Properties and Ligand Efficiencies | Journal of Medicinal Chemistry - ACS Publications, accessed April 30, 2025, https://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.1c00416
88. Michael D. Altman's research works | Merck & Co. and other places - ResearchGate, accessed April 30, 2025, https://www.researchgate.net/scientific-contributions/Michael-D-Altman-56114381
89. Epidermal ZBP1 stabilizes mitochondrial Z-DNA to drive UV-induced IFN signaling in autoimmune photosensitivity | bioRxiv, accessed April 30, 2025, https://www.biorxiv.org/content/10.1101/2024.01.23.576771v1.full-text
90. PF-06928215 (CAS Number: 2378173-15-8) | Cayman Chemical, accessed April 30, 2025, https://www.caymanchem.com/product/32515/pf-06928215
91. PF-06928215 | cGAS Inhibitor - MedchemExpress.com, accessed April 30, 2025, https://www.medchemexpress.com/PF-06928215.html
92. Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay | PLOS One, accessed April 30, 2025, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0184843
93. Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay - PubMed, accessed April 30, 2025, https://pubmed.ncbi.nlm.nih.gov/28934246/
94. H-151 | STING-specific inhibitor - InvivoGen, accessed April 30, 2025, https://www.invivogen.com/sting-inhibitor-h151
95. H-151 | STING Antagonist - MedchemExpress.com, accessed April 30, 2025, https://www.medchemexpress.com/h-151.html
96. The novel STING antagonist H151 ameliorates cisplatin-induced acute kidney injury and mitochondrial dysfunction - American Journal of Physiology, accessed April 30, 2025, https://journals.physiology.org/doi/full/10.1152/ajprenal.00554.2020

97. maia-s1a.htm - SEC.gov, accessed April 30, 2025, https://www.sec.gov/Archives/edgar/data/1878313/000156459022025709/maia-s1a.htm
98. S-1 - 06/08/2023 - MAIA Biotechnology, Inc., accessed April 30, 2025, https://ir.maiabiotech.com/sec-filings/all-sec-filings/content/0001193125-23-163582/0001193125-23-163582.pdf
99. 10-K - MAIA Biotechnology, Inc. (MAIA), accessed April 30, 2025, https://ir.maiabiotech.com/sec-filings/all-sec-filings/content/0000950170-23-009766/maia-20221231.htm
100. Australian Authorities Approve ImmuneSensor Therapeutics' Phase 1 Trial for cGAS Inhibitor IMSB301 - Patsnap Synapse, accessed April 30, 2025, https://synapse.patsnap.com/blog/australian-authorities-approve-immunesensor-therapeutics-phase-1-trial-for-cgas-inhibitor-imsb301
101. cGAS inhibitors/STING Antagonists(Ifm Tre) - Drug Targets, accessed April 30, 2025, https://synapse.patsnap.com/drug/b5ebd70283b4422a8ac61673c3405a29
102. Immune - Articles - Page 10 - BioWorld, accessed April 30, 2025, https://www.bioworld.com/articles/topic/250,520?page=10
103. WO2020087126A1 - Methods of treatment, prevention and diagnosis - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/WO2020087126A1/en
104. Ventus Therapeutics U.S., Inc. - IPqwery, accessed April 30, 2025, https://www.ipqwery.com/ipowner/en/owner/ip/6100521-ventus-therapeutics-us-inc.html?rgk=IPType&rvk=Patent&rgk=Jurisdiction&rvk=USPTO
105. US10633411B2 - Pharmaceutical targeting of a mammalian cyclic di-nucleotide signaling pathway - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/US10633411B2/en
106. ImmuneSensor Therapeutics 2025 Company Profile: Valuation, Funding & Investors, accessed April 30, 2025, https://pitchbook.com/profiles/company/343149-58
107. Rare diseases: Insights from landscape analysis of current research, spotlighting amyotrophic lateral sclerosis, Huntington's - ChemRxiv, accessed April 30, 2025, https://chemrxiv.org/engage/api-gateway/chemrxiv/assets/orp/resource/item/667cbfa501103d79c5390086/original/rare-diseases-insights-from-landscape-analysis-of-current-research-spotlighting-amyotrophic-lateral-sclerosis-huntington-s-disease-and-

myasthenia-gravis.pdf
108. Nanoscale materials at work: Mapping emerging applications in energy, medicine, and beyond - ChemRxiv, accessed April 30, 2025, https://chemrxiv.org/engage/api-gateway/chemrxiv/assets/orp/resource/item/6622bd8891aefa6ce1ebc7f5/original/nanoscale-materials-at-work-map**-emerging-applications-in-energy-medicine-and-beyond.pdf
109. Board of regents of the university of texas systemPatents | PatentGuru, accessed April 30, 2025, https://www.patentguru.com/assignee/board-of-regents-of-the-university-of-texas-system?page=19
110. EP3906229A4 - Inhibitors of cgas activity as ... - Google Patents, accessed April 30, 2025, https://patents.google.com/patent/EP3906229A4/en
111. Immunesensor Therapeutics, Inc. - IPqwery, accessed April 30, 2025, https://www.ipqwery.com/ipowner/en/owner/ip/4231949-immunesensor-therapeutics-inc.html?rgk=IPType&rvk=Patent&rgk=Jurisdiction&rvk=USPTO
112. U.S. Patent Application for STING AGONIST COMBINATION, accessed April 30, 2025, https://patents.justia.com/patent/20210380695
113. Ventus Therapeutics, Inc. - Drug pipelines, Patents, Clinical trials - Patsnap Synapse, accessed April 30, 2025, https://synapse-patsnap-com.libproxy1.nus.edu.sg/organization/3c5d873a30f5ea7c8e0c6e9ca0820d52
114. Ventus Therapeutics U.S., Inc. - IPqwery, accessed April 30, 2025, https://www.ipqwery.com/ipowner/en/owner/ip/6100521-ventus-therapeutics-us-inc.html?rgk=IPType&rvk=Patent&rgk=Jurisdiction&rvk=WIPO
115. Phase I clinical trial data of biopharma companies in 2024 - BioWorld, accessed April 30, 2025, https://www.bioworld.com/content/phase1-data-2024
116. accessed December 31, 1969, https://patents.justia.com/patent/20240270740
117. Ifm due incPatents | PatentGuru, accessed April 30, 2025, https://www.patentguru.com/assignee/ifm-due-inc
118. IFM Due, Inc. - IPqwery, accessed April 30, 2025, https://www.ipqwery.com/ipowner/en/owner/ip/5525817-ifm-due-inc.html
119. ( 12 ) United States Patent - googleapis.com, accessed April 30, 2025, https://patentimages.storage.googleapis.com/eb/9f/de/29db29e72dabad/US11168326.pdf