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CB1 Reverse Agonists: A Cheminformatic and Patent Landscape Study

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Abstract

The endocannabinoid system plays a crucial role in numerous physiological functions, making cannabinoid receptor 1 (CB1) an attractive target for therapeutic development. This review provides a systematic analysis of patent filings from 2019 to 2023 that focuses on small-molecule Cannabinoid Receptor Type 1 (CB1) reverse agonist. It begins with an overview of the endocannabinoid system, highlighting CB1's involvement in energy balance, pain regulation, and neuroinflammatory processes. The main section of the review examines fifteen patents covering diverse structural classes—such as pyrazoles, triazoles, and piperidines—designed to achieve high CB1 affinity and efficacy. Evaluation of these patents uncovers innovative scaffolds aimed at enhancing receptor selectivity, limiting central nervous system penetration, and improving pharmacokinetic characteristics. Many of the patented compounds target metabolic disorders, including obesity and type 2 diabetes, by modulating CB1 signaling in peripheral tissues. Other therapeutic areas addressed include chronic pain, neurodegenerative conditions, and substance use disorders. Each patent is analyzed for its inventive aspects, synthetic feasibility, and reported in vitro and in vivo results. Insights from industry expert interviews underscore ongoing challenges, such as maintaining a favorable safety profile, preventing neuropsychiatric side effects, and addressing formulation difficulties. The review concludes by highlighting emerging trends and suggesting future directions for Cannabinoid Receptor Type 1 (CB1) reverse agonist development. Recommendations include using structure–activity relationship studies to fine-tune central versus peripheral activity, applying advanced drug-delivery approaches, and incorporating biomarker-driven clinical strategies. By integrating recent patent data and expert perspectives, this review seeks to guide medicinal chemists and pharmacologists in advancing CB1-focused drug discovery.

Keywords: Cannabinoid signaling pathway, CB1 receptor, pharmacological reverse agonists, patent filings, metabolic disease management, CB1 antagonism

INTRODUCTION

Cannabis sativa preparations have been used for centuries to alleviate pain and muscle spasms, but scientific knowledge of cannabinoids has advanced significantly over the last 50 years. The pivotal isolation of Δ9-tetrahydrocannabinol (THC), the plant's main psychoactive component, spurred the development of new cannabinoids and ultimately led to the cloning of the CB1 receptor. The subsequent discovery of the CB2 receptor further broadened our understanding of the endocannabinoid system [1].

The identification of endogenous cannabinoids, particularly anandamide (AEA) and 2-arachidonoylglycerol (2-AG), provides the first clear evidence of a naturally occurring cannabinoid signaling network, with each ligand showing unique receptor affinities and physiological functions.

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Renewed interest in therapeutic phytocannabinoids, especially non-intoxicating cannabidiol (CBD), has fueled research into applications such as anti-inflammatory and anticancer treatments, as well as therapies for addiction and epilepsy. This combination of historical use, molecular discoveries, and ongoing research sets the stage for examining recent patent activities from 2019 to 2023 [2].

This review introduces readers to the core concepts of endocannabinoid biology while critically analyzing patents proposing new methods for targeting cannabinoid receptors. Innovations cover a wide range of conditions, including metabolic and liver disorders, obesity, diabetes, neurodegenerative and addictive diseases, autoimmune hepatitis, and skin inflammation [3, 4]. We discuss novel analogs and formulations, providing expert insights into their potential and outlining directions for future therapeutic developments in cannabinoid receptor modulation.

Overview of Cannabinoid Receptor 1 (CB1)

The endocannabinoid system is a complex regulatory network that controls many physiological processes, with CB1, a prototypical G protein–coupled receptor, playing a key role. CB1 primarily signals via Gi/o proteins but can also activate the Gs, Gq/11, and G12/13 pathways, reflecting its ability to influence diverse cellular outcomes, including neurotransmitter release and neurite growth. Structurally, the seven transmembrane helices change conformation upon ligand binding, driving selective signaling responses [5, 6].

CB1 is broadly expressed throughout the central nervous system, including excitatory and inhibitory neurons as well as glial cells, affecting synaptic transmission, neuronal excitability, and other neurological processes. This widespread distribution presents both therapeutic opportunities and challenges, thus emphasizing the need for precise ligand targeting. CB1 is also implicated in metabolic and inflammatory disorders, reinforcing its significance as a drug target [7].

Reverse Agonism in Drug Development

Reverse agonism has revealed that receptors can exhibit constitutive activity without ligands, with inverse agonists stabilizing the inactive receptor state. The two-state model proposed by Berg and Clarke describes inverse agonist action through the differences in equilibrium constants between active and inactive receptor conformations.

Relevance to CB1

Cannabinoid Receptor Type 1 (CB1) reverse agonist offer advantages over neutral antagonists by reducing basal receptor activity. For example, Inversago Pharma's development of peripherally restricted Cannabinoid Receptor Type 1 (CB1) reverse agonist targets metabolic disorders while minimizing central nervous system side effects, which is consistent with research from George Kunos at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), U.S. National Institutes of Health.

Therapeutic Potential and Challenges

Compounds, such as pimavanserin, demonstrate clinical utility in neuropsychiatric conditions by suppressing constitutive receptor activity. Inversago Pharma's INV-101 shows promise for treating Prader–Willi syndrome, a disorder associated with elevated CB1 activity. However, understanding receptor constitutively and ensuring safety remain key challenges [8, 9].

Patent Search Methodology and Trends

Methodology

Patents were retrieved from ipindia.com and the World Intellectual Property Organization (WIPO) Patentscope using targeted keywords, classification codes, and inventor/applicant information to capture comprehensive filings of Cannabinoid Receptor Type 1 (CB1) reverse agonist.

Trends

U.S. filings dominate, mostly published, but not yet granted, reflecting an active research landscape. There has been a shift from metabolic applications toward neuropsychiatric and central nervous system (CNS) disorders, alongside chemical scaffold refinement, to optimize efficacy and safety.

Geographic Distribution

While international patents were considered, U.S. institutions led to CB1 inverse agonist development [10].

Key Players

Major contributors include Inversago Pharma Inc., INSERM, and Université de Bordeaux, illustrating that interdisciplinary collaboration drives innovation.

Recent Patent Highlights

US 2023/0174493 A1

We focused on amorphous 3,4-diphenyl-4,5-dihydro-1H-pyrazole derivatives formulated as solid dispersions in high-glass-transition polymers (≥50 °C) to maintain non-crystalline drug states. This strategy aims to inhibit CB1 peripherally, preserving efficacy while reducing CNS side effects. Specific formulations (F1, F2, F5, F6, F8, and F18) include polymers, surfactants, and excipients, along with X-ray diffraction profiles.

WO 2019/234728 A1

Describes THCA- and CBDA-derived ligands with a common core and variable moieties designed for peripheral CB1/CB2 engagement. These analogs may act as agonists or antagonists and show potential in inflammatory, neurodegenerative, autoimmune, dermatologic, and cancer indications, including antiproliferative effects. The pharmaceutical composition and administration methods have also been disclosed.

WO 2021/189141 PCT/CA2021/050385

Covers amorphous solid dispersions of Formula 1(a) and Formula I compounds in high–Tg polymers. Drug-to-polymer ratios ranged from 1:2 to 10:1, with active loads of 15–60 wt.%. Formulation methods include solvent-based spray drying, acoustic mixing, extrusion, and ball milling, and are processed into oral dosage forms. The therapeutic focus is on metabolic disorders (obesity, diabetes, and fatty liver disease) with improved bioavailability and safety.

US 2019/0071465 A1

Highlights pregnenolone and related steroids as CB1 inhibitors for metabolic, inflammatory, cancer, neurodegenerative, addictive, and fibrotic disorders. Pregnenolone counteracts THC-induced CB1 activation without anxiety-like effects and extended-release formulations maintain therapeutic levels while limiting steroid perturbation.

US 2019/0352305 A1

Introduction of 6-chloropurine-based CB1 antagonists for fatty liver diseases, including Nonalcoholic Steatohepatitis (NASH) and alcoholic steatosis, either alone or in combination with other agents. Multistep synthesis yields piperazine/piperidine derivatives, and in vivo studies have shown a reduction in hepatic lipid accumulation, suggesting benefits for obesity and metabolic comorbidities.

CONCLUSION

A comprehensive review of patents on cannabinoid receptor modulators revealed a wide array of innovative compounds with diverse therapeutic applications. These modulators, characterized by complex molecular structures, such as imidazoles, triazoles, and dihydropyrazoles, demonstrate advanced strategies in drug design. They exhibit varied pharmacological activities, acting as antagonists, inverse agonists, or dual CB1/CB2 modulators, highlighting the intricate role of cannabinoid receptor signaling in conditions such as fibrogenesis, inflammation, and addiction.

Particular attention is given to the development of peripherally restricted CB1 antagonists as promising treatments for preventing and managing lower urinary tract symptoms (LUTS). Patents outline both therapeutic and preventive strategies, emphasizing the timing of the interventions. Combining CB1 inhibitors with adjunct therapies, including antidepressants or other CB1 modulators, offers an integrated approach for treating substance use and behavioral addictions, supported by patient monitoring via digital tools.

This review also emphasizes novel amorphous 3,4-diphenyl-4,5-dihydro-1H-pyrazole derivatives for kidney-related disorders, such as diabetic nephropathy and obesity-linked kidney disease. Solid dispersion techniques are employed to maintain the amorphous state and enhance therapeutic effectiveness. In addition, cannabinoid derivatives with specific carboxamide substitutions have been proposed as CB1 and CB2 inhibitors, broadening their potential clinical applications.

Overall, patents reflect the evolving landscape of cannabinoid therapeutics, showcasing innovative chemical strategies for a range of medical conditions. Future research should focus on optimizing pharmacokinetics and pharmacodynamics, improving therapeutic indices, identifying new clinical uses, and underscoring the continued promise of cannabinoid-based treatments.

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