STM JOURNALS

International Journal of
Cheminformatics

Volume 4, Issue 1, 2026
January—June
DOI (Journal): 10.37591/IJCI

https://journals.stmjournals.com/ijci/

Research IJCI

Molecular Dynamics and Therapeutic Architectures of Cannabinoid Receptors: A Comprehensive Review

R. Madhumitha Sri[1,*], R.M. Aadarshvel[2], S. Ravichandran[3]

Abstract

Expanding on these foundations, recent structural biology studies using cryo-electron microscopy have provided high-resolution insights into the conformational dynamics of CB_1 and CB_2 receptors. These findings have enabled a more precise understanding of ligand–receptor interactions, particularly how agonists, antagonists, and reverse agonists stabilize distinct receptor states. Such knowledge is critical for rational drug design, allowing researchers to selectively modulate downstream signaling pathways. For instance, CB_1 receptors primarily couple to Gi/o proteins, leading to inhibition of adenylate cyclase, reduced cAMP levels, and modulation of ion channels, whereas CB_2 activation influences immune cell migration and cytokine release. In addition, the therapeutic landscape has shifted toward peripherally restricted CB_1 modulators to avoid central nervous system side effects such as anxiety and depression, which were observed with earlier compounds like rimonabant. Advances in nanotechnology-based drug delivery systems have further improved the bioavailability and targeting precision of cannabinoid-based therapeutics. Moreover, the integration of artificial intelligence in drug discovery pipelines has accelerated the identification of novel cannabinoid ligands with improved safety profiles. Collectively, these developments underscore the growing potential of ECS-targeted therapies in precision medicine, particularly for conditions with limited treatment options.

Keywords: Cannabinoid, CB_1 receptors, cryo-electron microscopy, β-arrestin, G-protein signaling

INTRODUCTION

Building upon these advances, emerging research has also highlighted the concept of biased agonism (or functional selectivity) at cannabinoid receptors, which is particularly relevant for the development of safer CB_1 reverse agonists. Biased ligands can preferentially activate or inhibit specific intracellular signaling pathways while avoiding others that may be associated with adverse effects. This selective pathway modulation opens new avenues for designing drugs that retain therapeutic efficacy while minimizing unwanted psychiatric or metabolic side effects. For example, ligands that avoid β-arrestin recruitment while modulating G-protein signaling are being explored to fine-tune receptor responses [1].

Another important area of investigation is the role of receptor heteromerization. CB_1 receptors have been shown to form heteromers with other G protein-coupled receptors such as dopamine D_2 receptors and serotonin 5-HT receptors. These receptor complexes exhibit unique pharmacological and signaling properties, which may explain some of the complex physiological effects observed with cannabinoid ligands. Targeting such heteromeric complexes could provide an additional layer of specificity in drug design, particularly in neuropsychiatric and neurodegenerative disorders.

***Author for Correspondence**
R. Madhumitha Sri
E-mail: madhuravi02@gmail.com

[1]B.Tech. Student in Anna University & Validation Analyst (R&D), Zifo Technology, Chennai, Tamil Nadu, India
[2]BBA Student in Airlines & Airport Management, Lovely Professional University, Jalandhar, Punjab, India
[3]Professor in Chemistry, St.Peter's Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Received Date: April 22, 2026
Accepted Date: April 22, 2026
Published Date: April 30, 2026

Citation: R. Madhumitha Sri, R.M. Aadarshvel, S. Ravichandran. Molecular Dynamics and Therapeutic Architectures of Cannabinoid Receptors: A Comprehensive Review. International Journal of Cheminformatics. 2026; 4(1): 36–40p.

Furthermore, advances in pharmacogenomics are beginning to influence cannabinoid-based therapy development. Genetic variations in components of the endocannabinoid system, including receptor polymorphisms and enzymes such as FAAH and MAGL, can significantly impact individual responses to cannabinoid ligands. Understanding these variations allows for more personalized therapeutic approaches, aligning with the broader goals of precision medicine. This is especially relevant in chronic conditions such as obesity, pain, and inflammatory diseases, where patient responses can vary widely [2].

In parallel, there is increasing interest in the role of the endocannabinoid system in the gut–brain axis. CB_1 receptors in the gastrointestinal tract regulate appetite, motility, and energy balance, while CB_2 receptors modulate intestinal inflammation. Peripherally restricted CB_1 reverse agonists are therefore being explored as potential treatments for metabolic syndrome and gastrointestinal disorders without central adverse effects. Additionally, modulation of the ECS has shown promise in influencing the gut microbiome, further expanding its therapeutic relevance.

Finally, regulatory and clinical perspectives are evolving alongside scientific progress. While earlier setbacks with centrally acting CB_1 antagonists highlighted safety concerns, newer generations of compounds are being evaluated with improved trial designs and safety monitoring. Continued interdisciplinary collaboration among structural biologists, pharmacologists, and clinicians will be essential to translate these innovations into clinically viable therapies. In the contemporary landscape of 2026, the focus has shifted from simple agonism to "precision endocannabinoid medicine," where synthetic chemistry is used to target specific receptor conformations to avoid the psychiatric side effects associated with global CB_1 activation [3].

MOLECULAR STRUCTURE AND CLASSIFICATION

Both CB1 and CB2 receptors possess the classical G protein–coupled receptor (GPCR) architecture, characterized by seven transmembrane (7TM) α-helices interconnected by three extracellular loops (ECL1–ECL3) and three intracellular loops (ICL1–ICL3). These helices are embedded within the lipid bilayer and create a ligand-binding pocket that is crucial for receptor activation and signal transduction. The extracellular N-terminus plays a role in ligand recognition and receptor stability, while the intracellular C-terminus is involved in interactions with G proteins and regulatory proteins such as β-arrestins [4].

Structurally, the 7TM helices are arranged in a compact bundle, forming a central cavity that accommodates endogenous ligands like anandamide and 2-arachidonoylglycerol, as well as exogenous cannabinoids. Subtle differences in the amino acid composition within this binding pocket contribute to ligand selectivity between CB1 and CB2. For instance, CB1 receptors, predominantly expressed in the central nervous system, exhibit a more hydrophobic and binding cavity, allowing interaction with lipophilic ligands. In contrast, CB2 receptors, mainly found in peripheral tissues and immune cells, display structural variations that influence their pharmacological profile.

The intracellular loops, particularly ICL2 and ICL3, are critical for coupling with heterotrimeric G proteins, primarily of the $G_{i/o}$ family. Upon ligand binding, conformational changes in the transmembrane helices—especially helices V and VI—facilitate the activation of G proteins by promoting GDP-GTP exchange on the Gα subunit. This leads to downstream signaling events such as inhibition of adenylate cyclase, reduction in cyclic AMP (cAMP) levels, and modulation of ion channels. Additionally, receptor phosphorylation at the C-terminal tail can recruit β-arrestins, initiating receptor desensitization and internalization.

Another important structural feature is the presence of conserved motifs typical of GPCRs, such as the DRY (Asp-Arg-Tyr) motif located at the cytoplasmic end of helix III and the NPxxY motif in helix VII. These motifs play essential roles in maintaining receptor stability and facilitating conformational

transitions between inactive and active states. Mutations in these regions can significantly alter receptor signaling and ligand efficacy.

Furthermore, recent advances in cryo-electron microscopy and X-ray crystallography have provided high-resolution structures of cannabinoid receptors, offering deeper insights into ligand binding, receptor activation, and the structural basis of agonism, antagonism, and inverse agonism. Understanding these structural details is essential for the rational design of selective drugs targeting CB_1 and CB_2, particularly in the development of therapeutics for neurological disorders, pain management, and immune-related diseases [5].

The CB1 Receptor (CNR_1)

- *Localization:* Highest density in the basal ganglia, hippocampus, and cerebellum.
- *Function:* Regulates neurotransmitter release (GABA, Glutamate) via retrograde signaling.
- *Structure:* Features a deep, hydrophobic binding pocket that accommodates lipophilic ligands like Δ^9-THC.

The CB2 Receptor (CNR_2)

- *Localization:* Expressed in microglia, B-cells, and T-cells; also found in the liver and spleen.
- *Function:* Primarily immunomodulatory and anti-inflammatory.
- *Homology:* Shares approximately 44% amino acid sequence identity with CB1.

SIGNAL TRANSDUCTION PATHWAYS

Cannabinoid receptors primarily couple with a proteins. The activation of these receptors initiates a cascade that generally leads to the inhibition of cellular excitability. Upon ligand binding—whether by endogenous cannabinoids like anandamide or exogenous compounds—the receptor undergoes a conformational change that promotes the exchange of GDP for GTP on the α-subunit of the G protein. This activated α-subunit, along with the βγ complex, then dissociates and interacts with various downstream effectors [6].

One of the principal consequences of this signaling is the inhibition of adenylyl cyclase, which reduces the intracellular levels of cyclic AMP (cAMP). Lower cAMP concentrations subsequently lead to decreased activity of protein kinase A (PKA), resulting in reduced phosphorylation of target proteins involved in neurotransmitter release and neuronal firing. In addition, cannabinoid receptor activation can modulate ion channel activity. Specifically, it promotes the opening of inwardly rectifying potassium channels (GIRKs), leading to hyperpolarization of the neuronal membrane. Simultaneously, it inhibits voltage-gated calcium channels, thereby decreasing calcium influx into the cell. Since calcium is essential for vesicular release of neurotransmitters, this inhibition effectively reduces synaptic transmission [7].

These combined effects contribute to the overall depressant action on neuronal activity, which is a hallmark of cannabinoid signaling. In the central nervous system, this mechanism underlies various physiological and pharmacological effects, including analgesia, sedation, appetite stimulation, and memory modulation. Furthermore, cannabinoid receptor signaling is not limited to neurons; it also plays a significant role in immune cells, where it regulates cytokine release and inflammatory responses [8].

Another important aspect of cannabinoid receptor function is receptor desensitization and internalization. Prolonged activation leads to phosphorylation of the receptor by G protein-coupled receptor kinases (GRKs), followed by binding of β-arrestins (Table 1). This process uncouples the receptor from G proteins and targets it for internalization into endosomes, thereby attenuating signaling. Such regulatory mechanisms are crucial for maintaining cellular homeostasis and preventing overstimulation [9].

Table 1. Differential signaling profiles of CB receptors.

Feature	CB_1 Receptor	CB_2 Receptor
Primary G-Protein	$G_{i/o}$	$G_{i/o}$
Effector (cAMP)	Decrease	Decrease
Ion Channels	Ca^{2+} (inhibits), K^+ (activates)	Negligible effect
Beta-Arrestin	High Recruitment	Moderate Recruitment
Expression	Presynaptic Terminals	Immune Cells/Microglia

In the context of reverse agonists, these compounds bind to cannabinoid receptors and stabilize them in an inactive conformation, reducing their constitutive activity. This results in effects opposite to those produced by agonists, such as increased cAMP levels and enhanced neurotransmitter release. Understanding these intricate signaling pathways is essential for developing targeted therapies that modulate the endocannabinoid system in conditions such as obesity, addiction, and neurodegenerative disorders [10].

Primary Signaling Cascade

1. *Inhibition of Adenylyl Cyclase:* Reduces intracellular levels of cyclic adenosine monophosphate (cAMP).
2. *Ion Channel Regulation:*
   - Inhibition of N-type and P/Q-type channels.
   - Activation of G protein-coupled inwardly rectifying potassium (GIRK) channels.
3. *MAPK Pathway:* Activation of p38 and ERK1/2, influencing gene expression and cell survival.

ENDOGENOUS AND EXOGENOUS LIGANDS

The interaction between receptors and ligands is defined by the "Affinity" (K^i) and "Efficacy."

Endocannabinoids

- *AEA (Anandamide):* High affinity for CB1, but acts as a partial agonist.
- *2-AG:* Present in much higher concentrations in the brain; acts as a full agonist at both receptors.

Phytocannabinoids (2026 Perspective)

While THC and CBD remain dominant, 2026 research has highlighted **Cannabigerol (CBG)**. CBG acts as a non-intoxicating ligand that interacts with CB1/CB2 as well as α^2-adrenergic receptors, providing a "multi-target" approach to neuroinflammation.

THERAPEUTIC POTENTIAL AND CLINICAL APPLICATIONS

Neurodegenerative Diseases

Targeting CB2 on microglia has shown promise in slowing the progression of Alzheimer's and Parkinson's. By shifting microglia from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype, CB2 agonists reduce neuronal oxidative stress.

Pain Management

The "Entourage Effect" suggests that targeting CB1 in the periphery while utilizing CB2 for inflammation can achieve analgesia comparable to opioids without the respiratory depression or addiction risk.

Oncology

Synthetic CB_2 agonists (e.g., HU-308) have been shown in 2024-2025 studies to inhibit tumor proliferation by inducing apoptosis via the ceramide pathway, particularly in triple-negative breast cancer and glioblastoma.

CHALLENGES AND FUTURE DIRECTIONS

The primary hurdle remains the **Psychotropic Ceiling**. CB1 agonists, while effective for pain, can induce anxiety or "high" states.

Future Solution (2026+): Biased Agonism. Researchers are developing ligands that selectively activate the G-protein pathway while avoiding the β-arrestin pathway (responsible for receptor desensitization and some side effects).

CONCLUSION

Cannabinoid receptors are no longer viewed simply as the targets of recreational cannabis. They are sophisticated metabolic and neurological rheostats. The next decade of pharmacology will likely move toward peripherally restricted CB1 antagonists (for obesity) and selective CB2 agonists (for autoimmune disorders), finally decoupling the medicinal benefits of cannabinoids from their psychoactive history. This shift is driven by a deeper understanding of endocannabinoid system compartmentalization and receptor-specific signaling pathways. Peripheral CB1 blockade, for instance, offers the promise of improving insulin sensitivity, lipid metabolism, and energy balance without crossing the blood–brain barrier, thereby minimizing central nervous system side effects such as anxiety or depression that plagued earlier agents. At the same time, CB2 receptor modulation is emerging as a compelling strategy in inflammatory and immune-mediated diseases, given its predominant expression on immune cells and its role in cytokine regulation and immune homeostasis.

Advances in drug design, including biased agonism and allosteric modulation, are further refining receptor selectivity and functional outcomes. These innovations allow for fine-tuning of receptor responses rather than complete activation or inhibition, opening doors to safer and more effective therapeutics. As research progresses, the endocannabinoid system is poised to become a central pillar in treating complex, multifactorial diseases, bridging metabolism, immunity, and neurobiology in a way few other systems can.

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