Rewiring the endocannabinoid system pharmacology through the kinome.

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Abstract

The endocannabinoid system (ECS) orchestrates neural, immune, and metabolic homeostasis; however, its therapeutic translation has been persistently constrained by the psychoactive burden and pharmacodynamic liabilities associated with CB_1 and CB_2 receptor activation. Notably, endogenous cannabinoids fail to reproduce the psychotropic effects of phytocannabinoids, underscoring a fundamental disconnect between physiological ECS signaling and receptor-centric drug design. Beyond classical ligand–receptor paradigms, the ECS operates within kinase-regulated signaling networks that control receptor trafficking, intracellular signal integration, and endocannabinoid biosynthesis and degradation. This review reframes ECS pharmacology through the lens of the kinome, identifying MAPK, AMPK, PKA, PKC, and PI3K/Akt pathways as critical intracellular nodes amenable to therapeutic intervention. We evaluate emerging strategies—including ATP-competitive inhibitors, allosteric modulators, PROTACs, molecular glues, and dual-target hybrid compounds—that enable receptor-independent modulation of ECS function. Proof-of-concept studies across neuroinflammatory, metabolic, and tolerance-related models illustrate the translational potential of this approach. By positioning the kinome as a druggable interface, this framework advances ECS therapeutics beyond surface receptor engagement toward mechanism-informed, scalable, and precision-oriented interventions.

Keywords: Endocannabinoid system (ECS), Protein Kinase Signaling, Small-Molecule Therapeutics, Kinase Inhibitors and Modulators, Targeted Drug Development

1. Introduction

The endocannabinoid system (ECS) represents a fundamental homeostatic system that integrates neuronal signaling with immune and metabolic processes [1]. Beyond cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) receptor signaling, the ECS modulates intracellular pathways through lipid mediators, kinase activity, and GPCR crosstalk [2]. It fine-tunes neuronal excitability, immune cell dynamics, and energy homeostasis in response to environmental and physiological cues [3]. Dysregulation of ECS signaling contributes to neuroinflammation, metabolic disorders, and cancer, positioning the system as a critical therapeutic target [4].

While the ECS has been extensively examined through cannabinoid receptor signaling and endocannabinoid metabolism, its regulation by intracellular signaling cascades remains underexplored and conceptually underdeveloped [5]. Protein kinases critically modulate ECS activity by integrating extracellular cues into coordinated cellular responses that govern receptor signaling, endocannabinoid turnover, and downstream functional outcomes [6]. Despite this, most therapeutic strategies targeting the ECS have relied on direct modulation of cannabinoid receptors or metabolic enzymes [7-9], thereby overlooking the potential of kinase-directed interventions to fine-tune ECS function with greater specificity.

Protein kinases, including mitogen-activated protein kinases (MAPKs), protein kinase A (PKA), protein kinase C (PKC), and AMP-activated protein kinase (AMPK), act as central modulators of ECS activity by controlling receptor phosphorylation, intracellular trafficking, and signal propagation [10-13]. Their dysregulation has been implicated in a range of pathological conditions [14], including neurodegenerative disorders, psychiatric diseases, chronic inflammation, and cancer [15-18]. For example, MAPK pathways mediate cannabinoid-induced neuroinflammatory responses [19, 20], while AMPK functions at the interface of ECS and metabolic regulation, making kinase-targeting strategies a compelling yet

underutilized approach for ECS-based therapies. The therapeutic relevance of kinases in ECS modulation raises critical questions about the feasibility of kinase inhibitors or activators as indirect modulators of cannabinoid receptor function.

The emergence of small-molecule kinase inhibitors, marked by imatinib's landmark approval in 2001, has profoundly reshaped targeted therapy, predominantly within oncology but also expanding into inflammatory and autoimmune conditions [21]. Currently, 80 FDA-approved kinase inhibitors target approximately two dozen kinases, highlighting the therapeutic versatility of this drug class [22]. However, their application to modulate ECS(ECS)-related pathways remains limited. Small molecules present significant therapeutic advantages, including enhanced selectivity, structural tunability, and precise intracellular signaling modulation without direct receptor activation [23], thereby reducing undesirable psychoactive effects. Leveraging kinase inhibitors for ECS modulation thus offers a compelling and underexplored therapeutic opportunity.

Given the broad involvement of ECS dysregulation in multiple disease states, including neurodegenerative, inflammatory, and metabolic disorders [3, 24, 25], kinase-based modulation may provide versatile therapeutic strategies. For example, pharmacological targeting of MAPK signaling pathways could mitigate ECS-driven pathology, such as neuroinflammation, without directly engaging cannabinoid receptors (CB1 or CB2). Specific MAPK inhibitors, such as SB203580 (p38 inhibitor) [26, 27] and SP600125 (JNK inhibitor) [28], effectively reduce microglial activation and cytokine production, key processes in neuroinflammation. Cannabinoid-associated metabolic disturbances are primarily mediated through CB1 receptor activation, leading to impaired lipid metabolism [29] and reduced insulin sensitivity [30]. AMP-activated protein kinase (AMPK) activators, such as metformin or AICAR, have been shown to enhance insulin sensitivity and stimulate fatty acid oxidation [31, 32]. Thus, AMPK activators may counter cannabinoid-induced metabolic dysfunction by influencing pathways downstream

or independent of CB1 receptor signaling. Together, these examples illustrate how kinase-targeted interventions could offer precise, receptor-independent modulation of ECS signaling, potentially restoring homeostasis across diverse pathological conditions.

Regardless of these promising avenues, significant challenges remain in the development of kinase-targeting small-molecule therapies for ECS-related diseases. Selectivity remains a primary concern, as many kinase inhibitors exhibit off-target effects that limit their therapeutic utility [33, 34]. Additionally, the development of drug resistance, particularly in oncology [35] and neurodegenerative diseases [36], necessitates novel strategies to enhance the durability of kinase-targeting therapies. Furthermore, for ECS-related disorders affecting the central nervous system, achieving effective drug concentrations through optimized blood-brain barrier penetration represents another critical challenge. Addressing these issues is essential to fully leverage the therapeutic promise of kinase modulation within the ECS.

This review explores the emerging intersection between kinase signaling pathways and the ECS(ECS), highlighting the therapeutic potential of small-molecule kinase modulators. We discuss critical kinase pathways implicated in ECS regulation, assess the current landscape of kinase-targeting drug development, and outline the existing challenges alongside future directions for clinical translation. By shifting focus from traditional receptor-centric approaches toward precise, pathway-specific modulation, we propose a refined therapeutic framework for ECS-related diseases. A deeper understanding of kinase-ECS crosstalk promises innovative therapeutic strategies for disorders driven by ECS dysregulation.

2. The ECSand its molecular landscape

The ECS(ECS) is an intricate signaling network that extends far beyond its canonical association with CB1 and CB2 receptors, functioning as a biochemical integrator that regulates

neuronal excitability, immune responses, and metabolic homeostasis [37-39]. While traditionally viewed through the lens of ligand-receptor interactions, the ECS operates within a broader molecular framework in which kinases ERK1/2, p38 MAPK, c-Jun N-terminal Kinase, Protein Kinase A, Akt/PKB, AMPK, Cyclin-dependent kinase 5, Focal Adhesion Kinase, Src-family Kinases play a decisive role in modulating receptor activity, intracellular signaling, and enzymatic turnover [13, 40-47]. The ECS(ECS) is tightly regulated by kinase-driven phosphorylation events that shape receptor signaling, endocannabinoid metabolism, and cellular responses. Yet, the therapeutic potential of this kinase–ECS crosstalk remains unexplored. As kinome-targeting strategies evolve beyond oncology [48-50], uncovering how specific kinases modulate ECS dynamics could reveal novel, pathway-selective opportunities for intervention—expanding cannabinoid pharmacology beyond receptor-centric approaches.

Central to the endocannabinoid system, CB1 and CB2 are its most extensively characterized receptors—class A G protein-coupled receptors (GPCRs) that initiate intracellular signaling through ligand-induced conformational changes and subsequent G protein coupling [51, 52]. CB1, widely distributed in the central nervous system, modulates synaptic transmission by inhibiting adenylate cyclase activity, reducing cAMP levels, and regulating ion channels [53, 54]. Its functional consequences range from neuroprotection and plasticity to behavioral modulation [55-59], but chronic activation often leads to receptor desensitization, an adaptive response driven by phosphorylation events mediated by protein kinase A (PKA), protein kinase C (PKC), and G protein-coupled receptor kinases (GRKs) [60]. From a kinome perspective, CB1 integrates into complex intracellular networks, including ERK1/2 and Akt signaling cascades, highlighting the broader relevance of kinase activity in shaping cannabinoid responses.

Although structurally homologous to CB1, the CB2 receptor displays distinct physicochemical and pharmacological features aligned with its peripheral specialization. It is predominantly

expressed in immune cells and peripheral tissues, where its activation orchestrates anti-inflammatory responses by modulating cytokine release, immune cell trafficking, and resolution of inflammation [61-63]. Unlike CB1, CB2 exhibits lower constitutive activity and a more restricted expression profile than CB1, which contributes to its peripheral selectivity, lack of psychotropic effects, and favorable safety margin [64, 65]. From a kinome perspective, CB2 signaling engages mitogen-activated protein kinase (MAPK) cascades, including ERK1/2, p38, and JNK, as well as PI3K/Akt and NF-κB pathways—positioning it as a key node in the regulation of immune and inflammatory responses [41, 66-69]. Phosphorylation by G protein-coupled receptor kinases (GRKs) and other kinases also governs CB2 desensitization and internalization, although with distinct kinetics and sensitivity compared to CB1 [63, 70]. These properties position CB2 as a compelling target for kinase-informed therapies in immunomodulation, neuroinflammation, and chronic pain, where peripheral selectivity and minimal CNS side effects are clinically desirable.

Beyond CB1 and CB2, several non-canonical components of the ECS—including transient receptor potential vanilloid 1 (TRPV1), peroxisome proliferator-activated receptors (PPARs), and orphan G protein-coupled receptors such as GPR55 and GPR18—contribute to the functional landscape of endocannabinoid signaling [71]. These receptors intersect with diverse kinase pathways: TRPV1 activity is modulated by phosphorylation via PKC and MAPKs, linking it to nociceptive and inflammatory signaling [72]; PPARs, as nuclear receptors, are regulated by upstream kinases like AMPK and ERK, influencing lipid metabolism and inflammation [73]; GPR55 engages with RhoA and ERK signaling, implicating it in processes such as osteogenesis and cancer progression [74, 75]; and GPR18, though less characterized, has been associated with immune modulation and may interact with intracellular kinase cascades [76]. Understanding how these non-classical ECS components interface with the

kinome may uncover additional targets for selective modulation of ECS-related physiology and pathology.

ECS activity is equally dependent on the dynamic balance between endocannabinoid biosynthesis and degradation, a process controlled by enzymatic machinery subject to kinase regulation [77]. The principal endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are synthesized on demand through lipid remodeling enzymes such as N-acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL), respectively. Their degradation, primarily mediated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), dictates local endocannabinoid tone and signaling duration [78]. Importantly, these enzymatic pathways are dynamically regulated by kinase-driven phosphorylation, which modulates their activity, localization, and signaling interactions. For example, ERK1/2 activation can influence FAAH expression, altering AEA degradation rates [79], while AMPK activation may influence endocannabinoid signaling by modulating metabolic pathways that regulate CB1 receptor activity rather than directly altering lipid precursor availability [80].

Beyond GPCR and metabolic roles, endocannabinoid signaling intersects with kinase-regulated neurotransmitter systems, modulating serotonergic, dopaminergic, and purinergic pathways via receptor crosstalk and signaling convergence [81, 82]. The interaction between CB1 and serotonin 5-HT1A receptors, for instance, modulates ERK and p38 MAPK activity, impacting mood regulation and stress responses [83, 84]. Similarly, adenosine A2A receptor signaling, which intersects with CB1 at the striatal level, is governed by PKA and MAPK activity [85], illustrating the broader kinase-dependent landscape in which cannabinoid pharmacology is embedded. These interactions highlight that cannabinoid effects arise not in isolation, but through kinase-driven signaling networks shaping their biological outcomes.

3. Kinome modulation of the endocannabinoid system

Targeting the kinome offers a pathway-selective strategy to modulate the ECS without directly engaging cannabinoid receptors—an approach that may overcome limitations such as desensitization, psychoactivity, and receptor redundancy [86]. Several classes of small-molecule therapeutics have emerged to selectively modulate kinase activity associated with ECS signaling, each with distinct mechanistic and translational profiles [87]. To operationalize kinase-directed modulation of the ECS, several mechanistically distinct therapeutic classes have emerged. ATP-competitive inhibitors disrupt phosphorylation cascades relevant to ECS signaling, including MAPK, AMPK, PKA, and PKC, without engaging cannabinoid receptors directly [88]. Allosteric modulators act at non-catalytic sites to fine-tune kinase or receptor function with enhanced selectivity [89]. Targeted protein degraders—including PROTACs and molecular glues—enable catalytic elimination of kinases and non-enzymatic regulators implicated in ECS dysregulation [90, 91]. Finally, hybrid dual-target compounds integrate cannabinoid receptor ligands and kinase modulators within a single scaffold to synergize membrane and intracellular modulation [92]. The following sections dissect each strategy's mechanism of action, pharmacological scope, and translational relevance to ECS-related disorders.

3.1 ATP-competitive kinase inhibitors

ATP-competitive inhibitors are among the most clinically validated small molecules, targeting the conserved ATP-binding cleft of kinases to block phosphorylation and downstream signaling [93]. Beyond catalytic inhibition, their binding can induce conformational changes that modulate kinase dynamics and regulatory interactions, conferring functional selectivity [94]. While most bind reversibly, covalent and irreversible variants have been designed to enhance

target engagement and prolong pharmacodynamic effects. In the ECS(ECS), key kinases such as ERK1/2, p38, JNK, PKA, PKC, AMPK, and CDK5—implicated in receptor regulation, immune modulation, metabolic control, and neuroplasticity—are susceptible to ATP-competitive inhibition. By targeting these kinases, such inhibitors offer a precise, indirect means of modulating ECS activity in disease contexts marked by its dysregulation [95].

MAPK Pathways and ECS Crosstalk

Mitogen-activated protein kinases (MAPKs)—including ERK1/2, JNK, and p38—are key effectors of endocannabinoid receptor signaling, linking CB1 and CB2 activation to transcriptional regulation, cytokine production, and cell fate decisions [11, 96]. CB1 engagement promotes ERK1/2 phosphorylation via G_i/o-dependent transactivation of receptor tyrosine kinases, supporting neuronal differentiation and neurite outgrowth [97]. In contrast, CB2 preferentially activates p38 and JNK, driving proinflammatory cytokine release and chemotaxis in immune cells [98]. This signaling convergence has therapeutic implications: MAPK inhibitors such as selumetinib (MEK1/2), SB203580 (p38), and SP600125 (JNK) attenuate ECS-associated inflammatory responses in astrocytes and microglia [99, 100]. These findings highlight MAPK pathways as critical nodes for pharmacological modulation of ECS activity in neuroinflammatory and immune-related disorders.

PKA and PKC in receptor desensitization and synaptic modulation

Protein kinase A (PKA) and protein kinase C (PKC) are central to cannabinoid receptor regulation, mediating desensitization and synaptic adaptation [101, 102]. While CB1 activation acutely suppresses adenylyl cyclase and reduces cAMP, sustained stimulation induces receptor phosphorylation via PKA and PKC, leading to desensitization, internalization, and tolerance [43]. Pharmacological inhibition of these kinases with H89 (PKA) and Gö6983 (PKC) prevents CB1 desensitization in neuronal systems, enhancing G-protein coupling and preserving receptor responsiveness [44]. These findings support PKA/PKC inhibition as a viable approach to sustain ECS signaling under conditions of chronic receptor activation, with implications for pain, addiction, and neurodegenerative disorders.

AMPK and Metabolic Modulation

AMP-activated protein kinase serves as a key metabolic sensor and modulator of ECS-driven energy balance. Central CB_1 receptor activation inhibits hypothalamic AMPK, promoting hyperphagia and lipid accumulation, while peripheral CB_1 signaling suppresses hepatic AMPK, contributing to insulin resistance and steatosis[103-106]. Pharmacological AMPK activation with agents such as AICAR or metformin analogs reverses these effects, restoring metabolic homeostasis and improving insulin sensitivity in ECS-dysregulated models [107-109]. Although not ATP-competitive, these activators act through allosteric or AMP-mimetic mechanisms, enabling ECS modulation independently of direct cannabinoid receptor targeting [110].

CDK5 and ECS plasticity

Cyclin-dependent kinase 5 (CDK5), though structurally divergent from other CDKs, is essential for neural development and synaptic remodeling [111]. CB1 receptor signaling has been shown to modulate CDK5 activity through p25 generation, leading to phosphorylation events that regulate receptor internalization and desensitization, particularly in the context of long-term synaptic depression and addiction-related neuroplasticity. [112]. Palbociclib, a selective CDK4/6 inhibitor with minimal activity against other CDKs, has recently been shown to bind and inhibit the non-kinase protein STING with high affinity, suggesting potential immunomodulatory properties beyond its canonical cell cycle effects; such off-target activity may intersect with ECS-regulated synaptic functions, though this remains to be fully elucidated. [113].

Advantages and Limitations

ATP-competitive kinase inhibitors are supported by extensive pharmacological validation, with well-defined scaffolds, favorable pharmacokinetics, and established clinical use—particularly in oncology and inflammatory disorders [114]. Several compounds are FDA-approved, facilitating repurposing opportunities for ECS-related conditions [115]. However, their utility is constrained by limited selectivity due to the conserved nature of the ATP-binding cleft across the kinome, increasing the risk of off-target effects and systemic toxicity [116]. Chronic inhibition of key signaling nodes may also trigger adaptive responses, including pathway rewiring and compensatory signaling, reducing long-term efficacy [117]. Within the ECS, these challenges are compounded by the absence of inhibitors specifically optimized for it signaling architecture, highlighting the need for rational design strategies that account for isoform specificity, spatial dynamics, and network topology in ECS-active tissues.

Table 1. Clinically approved ATP-competitive kinase inhibitors with potential implications for ECS-related pathophysiology

Inhibitor Name	Primary Kinase Targets	Mechanism of Action	FDA-Approved Indications	Potential ECS Relevance
Osimertinib	EGFR (mutant forms)	Irreversible inhibition of mutant EGFR via ATP-binding site	NSCLC with EGFR mutations	EGFR-ERK cross-talk may affect ECS tone in glioma
Dasatinib	SRC, BCR-ABL, others	Broad tyrosine kinase inhibitor	CML, ALL	SRC is implicated in CB1 receptor trafficking
Ruxolitinib	JAK1/2	JAK-STAT pathway inhibition via ATP-competitive binding	Myelofibrosis, polycythemia vera	JAK-STAT links to ECS cytokine regulation
Ibrutinib	BTK, EGFR (weak)	BTK inhibition in B-cell signaling	B-cell malignancies	BTK activity can influence ECS in immune cells
Palbociclib	CDK4/6	Inhibits CDK-mediated cell cycle progression	ER+ breast cancer	Off-target CDK5 inhibition affects CB1 synaptic regulation
Sunitinib	VEGFR, PDGFR, KIT, FLT3	Multi-kinase inhibition	Renal cell carcinoma, GIST	Angiogenesis and ECS both regulate tumor microenvironment
Lorlatinib	ALK, ROS1	Inhibits fusion kinases in NSCLC	ALK+ NSCLC	ALK signaling may intersect with CB2 in brain tumor models

3.2 PROTACs (Proteolysis-Targeting Chimeras)

PROTACs are heterobifunctional molecules that induce targeted protein degradation by harnessing the ubiquitin–proteasome system. Each PROTAC contains a ligand for the protein of interest (POI), an E3 ligase recruiter, and a linker. Upon entering the cell, they promote ternary complex formation between the POI and E3 ligase, resulting in polyubiquitination—primarily via K48 chains—and subsequent proteasomal degradation.

PROTACs are heterobifunctional molecules that induce selective protein degradation by co-opting the ubiquitin–proteasome system. They consist of a ligand for the protein of interest (POI), an E3 ligase recruiter, and a linker. Upon cellular entry, PROTACs facilitate ternary

complex formation between the POI and E3 ligase, leading to K48-linked polyubiquitination and subsequent proteasomal degradation [118]. Unlike conventional inhibitors that transiently block activity, PROTACs catalytically eliminate the entire protein, enabling sustained depletion and targeting of non-enzymatic or scaffolding proteins previously considered undruggable [119]. This strategy offers several advantages: irreversible target removal, substoichiometric efficacy, and the ability to bypass active-site dependency—broadening therapeutic scope to include regulatory proteins implicated in ECS signaling [120, 121].

Kinase-Directed PROTACs as Emerging Tools for ECS Regulation

Originally designed to degrade oncogenic kinases, PROTACs are now being explored to target kinases that modulate ECS signaling, including ERK1/2, CDK5, AMPK, and FAK. These kinases regulate ECS-linked processes such as neuroinflammation, synaptic plasticity, and metabolic control, making them suitable for proteasomal degradation via proximity-induced mechanisms [45]. ERK1/2, activated downstream of CB1 and CB2 receptors, modulates glial reactivity and cytokine release; selective degradation may attenuate neuroinflammation while sparing basal MAPK activity—an advantage over ATP-competitive inhibitors [66, 122]. CDK5, implicated in CB1 receptor desensitization and synaptic remodeling, has been effectively targeted by PROTACs to modulate cannabinoid tolerance [45]. By promoting catalytic degradation, PROTACs enable intermittent dosing with sustained effects, reducing off-target toxicity. Their ability to bind non-catalytic sites overcomes resistance from ATP-binding mutations, a common limitation of classical kinase inhibitors[123]. In ECS-enriched malignancies, PROTACs may suppress oncogenic signaling via downstream kinase degradation, without activating cannabinoid receptors—offering a receptor-independent, precision-based therapeutic strategy for neurological, metabolic, and neoplastic disorders [124-126].

Challenges and limitations

Despite their therapeutic promise, PROTACs face key limitations. Their high molecular weight (700–1,100 Da) restricts membrane permeability, limits oral bioavailability, and impairs blood–brain barrier penetration—hindering CNS-targeted ECS applications. Although advances in linker chemistry and polarity optimization have improved drug-like properties, most PROTACs remain confined to peripheral or oncologic contexts [127]. Tissue-selective degradation is further constrained by reliance on endogenous E3 ligase expression [128]. Clinically used ligases, such as cereblon (CRBN) and von Hippel–Lindau (VHL), display heterogeneous expression across ECS-relevant cell types, including astrocytes, microglia, and peripheral immune cells [129]. Recruitment of alternative ligases—such as DCAF15, RNF114, or KEAP1—may improve cellular specificity and expand applicability. Finally, unintended proteome remodeling remains a concern [130]. Off-target ubiquitination, particularly at high concentrations or with sustained exposure, underscores the need for systematic proteomic and transcriptomic profiling to ensure selectivity and safety in clinical translation [131].

Table 2. Selected PROTACs targeting kinases and epigenetic regulators with potential relevance to ECSmodulation.

PROTAC Name	Target Protein	Recruiting E3 Ligase	Mechanism of Action	Potential ECS Relevance	Development Stage
ARV-771	BRD4 (bromodomain-containing)	VHL	Degrades BRD4; suppresses oncogenic transcriptional programs	BRD4 may modulate neuroinflammation downstream of ECS	Preclinical; oncology
dCDK5-1	CDK5	CRBN	Induces degradation of CDK5; disrupts phosphorylation-linked plasticity	CDK5 involved in CB1 desensitization and addiction	Preclinical; ECS-relevant in vitro
MS147	EZH2/EED (PRC2 complex)	VHL	Targeted degradation of PRC2 components; epigenetic reprogramming	PRC2 regulates ECS-linked epigenetic plasticity in neurons	Preclinical; CNS studies
ARV-110	Androgen Receptor (AR)	CRBN	Degrades AR; inhibits AR signaling in prostate cancer	Hormonal-ECS crosstalk in metabolic and prostate disorders	Phase I/II clinical trials
dERK1/2 PROTACs	ERK1/2 (MAPK pathway)	VHL or CRBN	Degrades ERK1/2 to attenuate MAPK signaling in inflammation and cancer	ERK1/2 is a key effector of CB1/CB2 signaling	Experimental; proof-of-concept

3.3 Allosteric Strategies for ECS Modulation

Allosteric modulators regulate protein function by binding to non-catalytic sites, inducing conformational changes that enhance (PAMs) or inhibit (NAMs) activity. Unlike ATP-competitive inhibitors, they offer greater selectivity, reduced off-target effects, and partial modulation of signaling intensity [132]. While predominantly studied at cannabinoid receptors—particularly CB1—emerging data support the allosteric targeting of intracellular effectors within ECS pathways [133]. Regulatory kinases such as ERK1/2, PKA, and AMPK possess defined allosteric pockets, providing opportunities for fine-tuned modulation of ECS-linked signaling without disrupting basal activity [134-136]. CB1 allosteric ligands like Org27569, PSNCBAM-1, and GAT211 further validate this approach, altering receptor conformation, ligand affinity, and downstream signaling dynamics [137-139]. Notably,

Org27569 enhances orthosteric ligand binding yet attenuates ERK1/2 activation, exemplifying the potential for pathway-selective ECS modulation via allosteric control of key signaling nodes [140].

Multiple kinases involved in ECS signaling possess allosteric sites that enable selective pathway modulation. ERK1/2 activity can be attenuated via inhibitors targeting docking domains such as the D-recruitment site (DRS), disrupting ECS-related MAPK signaling with improved specificity and reduced cytotoxicity [141], as demonstrated by compounds like SCH772984 and Ulixertinib. PKA, critical for CB1 desensitization and metabolic regulation, can be modulated allosterically through disruption of regulatory subunit interactions or AKAP binding [142, 143], allowing localized inhibition without compromising global cAMP signaling—a strategy particularly relevant to synaptic and mitochondrial ECS regulation [144]. AMPK, a metabolic integrator under ECS control, is activated allosterically by ligands such as PF-06409577 and compound 991, which enhance Thr172 phosphorylation while avoiding off-target effects seen with AMP mimetics [145].

Advantages of allosteric modulation in ECS pharmacology

Allosteric modulation confers key advantages in ECS-targeted therapy by engaging non-conserved sites, improving isoform selectivity, and minimizing off-target effects [94, 146]. Unlike orthosteric or ATP-competitive inhibitors, allosteric agents enable graded regulation while preserving basal signaling—critical in homeostatic systems where both excess and deficiency are deleterious [147, 148]. Their pharmacodynamic profile allows flexible dosing, sustained engagement, and reduced risk of receptor or kinase downregulation [133]. In disorders characterized by subtle ECS imbalance, such precision may offer an improved therapeutic window.

Limitations and translational barriers

Despite their promise, allosteric modulators face significant development challenges. The structural variability and low conservation of allosteric sites complicate ligand design and require high-resolution structural data for selectivity [149]. Limited availability of scalable screening platforms further constrains discovery and validation. Functional efficacy is also context-dependent, influenced by receptor conformation, endogenous ligand occupancy, cell-type specificity, and post-translational modifications [150]. In the ECS, a major barrier is the paucity of validated allosteric sites on key kinases [151, 152]. While MAPK and AMPK pathways offer *proof-of-concept*, modulation of kinases such as CDK5, GSK3β, and PI3K remains poorly characterized, underscoring the need for targeted structural and pharmacological exploration.

Table 3. Selected allosteric modulators of kinase signaling with potential relevance to ECSregulation

Modulator Name	Target Protein	Allosteric Mechanism	Potential ECS Relevance	Development Stage
MK-2206	AKT (Protein Kinase B)	Binds pleckstrin homology (PH) domain to inhibit membrane localization	AKT involved in CB1/CB2 survival signaling and synaptic plasticity	Phase I/II clinical trials (oncology)
GDC-0068 (Ipatasertib)	AKT1/2/3	Allosteric inhibition of AKT activation via PH domain engagement	Inhibits pro-survival pathways downstream of ECS activation in cancer	Phase II trials (prostate, breast cancer)
STO-609	CaMKKβ (Calmodulin-dependent Kinase Kinase β)	Inhibits upstream kinase required for AMPK activation	Disrupts AMPK-CaMKKβ link; affects metabolic ECS regulation	Preclinical tool compound
CCG-203971	RhoA/MRTF/SRF Pathway (via ROCK kinase)	Allosteric modulation of Rho/MRTF signaling; reduces inflammatory gene expression	Modulates pro-inflammatory ECS signaling in glial cells	Preclinical; fibrosis and inflammation models
PF-4708671	S6K1 (Ribosomal Protein S6 Kinase)	Inhibits autoinhibitory region of S6K1 to reduce mTOR signaling	Downstream target of CB1–mTOR axis in neurodevelopment and plasticity	Experimental; neuroscience models

3.4 Molecular glues and targeted degraders

Molecular glues represent a distinct class of small-molecule degraders that induce proteasomal degradation through monovalent binding. Unlike PROTACs, they stabilize transient interactions between target proteins and E3 ligases [153], enabling ubiquitination without the need for bifunctional architecture [154]. Initially identified via phenotypic screens, molecular glues have demonstrated clinical efficacy in hematologic malignancies [155]—most notably the immunomodulatory imides (IMiDs) lenalidomide and thalidomide, which promote degradation of Ikaros and Aiolos via CRBN recruitment[156]. Recent developments have expanded their applicability to kinases, transcriptional regulators, and scaffolding proteins, several of which intersect with signaling pathways modulated by the ECS[157].

Potential applications of molecular glues in ECS-modulated signaling

While no ECS-specific molecular glues are clinically available, their mechanistic rationale is strong. Kinases such as ERK1/2, CDK5, GSK3β, and PI3K-related scaffolds—key regulators of cannabinoid signaling—represent promising targets for neosubstrate-directed degradation. CDK5, in particular, implicated in CB_1 desensitization and addiction-related plasticity, has shown vulnerability to cereblon-based glue-induced degradation, enabling sustained pathway suppression without continuous inhibition [158]. Neuroinflammation, a key ECS-regulated process, offers further therapeutic opportunities. In glial cells, ECS signaling modulates transcriptional programs via kinase-controlled hubs such as NF-κB, STAT3, and AP-1, which are also influenced by phytocannabinoids through Nrf2 and MAPK pathways [159]. Molecular glues targeting upstream kinases or transcriptional co-regulators may modulate ECS tone and exert sustained anti-inflammatory effects without receptor engagement.

Limitations and Developmental Gaps

Despite their conceptual appeal, molecular glues remain in early stages of development, and several challenges must be addressed before they can be applied to ECS pharmacology [160]. The identification of suitable neosubstrate–E3 ligase pairs is currently empirical and not easily predicted by structure alone. Moreover, glue activity is highly context-dependent, influenced by local protein concentrations, post-translational modifications, and cellular proteostasis capacity. A key limitation is the paucity of validated E3 ligases in ECS-relevant cell types. Most molecular glue strategies depend on CRBN or DCAF15, whose expression across glia, neurons, and immune subsets remains heterogeneous and poorly defined. Advancing ECS-targeted applications will require the development of cell type–specific degradation platforms,

potentially guided by single-cell proteomics and E3 ligase profiling. Safety considerations also remain paramount, including off-target proteome remodeling and unanticipated transcriptional reprogramming. Given that glues induce novel protein–protein interactions, comprehensive interactome mapping will be critical to mitigate adverse effects, particularly within the CNS.

Limitations and future directions for molecular glues in ECS pharmacology

Despite their mechanistic appeal, molecular glues remain in early development, with several translational barriers. Identification of compatible neosubstrate–E3 ligase pairs is largely empirical and poorly predicted by structural features. Glue activity is highly context-dependent, shaped by local protein abundance, post-translational modifications, and proteostasis dynamics [161]. A key limitation is the absence of validated E3 ligases in ECS-relevant cell types, with current approaches dependent on CRBN or DCAF15, whose expression is variable and poorly defined. Advancing ECS-targeted degradation requires cell type–specific platforms guided by single-cell proteomics. Safety concerns remain, as molecular glues may trigger off-target degradation and transcriptional reprogramming through neomorphic interactions. [162]. Interactome mapping will be key to minimizing off-target effects, particularly in the CNS. Molecular glues enable selective degradation of ECS-regulatory proteins beyond the scope of traditional inhibitors and hold promise for future application in neuroinflammation, psychiatry, and metabolic disease.

Table 4. Representative molecular glues with potential relevance to ECSregulation.

Compound Name	Primary Target(s)	Mechanism of Action	Potential ECS Relevance	Development Stage
Thalidomide	IKZF1/3 (via CRBN)	Promotes CRBN-mediated degradation of transcription factors	IKZF1/3 regulate neuroimmune responses relevant to ECS tone	FDA-approved (leprosy, multiple myeloma)
Lenalidomide	IKZF1/3 (via CRBN)	Enhances CRBN–IKZF complexation and proteasomal degradation	Modulates inflammation pathways indirectly influencing ECS signaling	FDA-approved (hematologic malignancies)
CC-885	GSPT1 (via CRBN)	Induces GSPT1 degradation through E3 ligase recruitment	Regulates translation termination factors with possible ECS impact in cancer	Preclinical; tool compound
Indisulam	RBM39 (via DCAF15)	Facilitates RBM39 ubiquitination via DCAF15 complex formation	Splicing factor control may affect ECS gene expression in glial cells	Phase I/II clinical evaluation
BI-3802	BCL6 (transcriptional repressor)	Self-assembles BCL6 dimers into a degradable polymer	BCL6 involved in immune memory; may shape ECS-immune interactions	Preclinical; proof-of-concept degrader

3.5 Hybrid dual-target molecules: convergent modulation of kinases and the ECS

Hybrid dual-target molecules represent an advanced strategy in rational drug design, wherein a single chemical entity is engineered to simultaneously modulate cannabinoid receptors and intracellular kinases. This approach capitalizes on the systems-level organization of the ECS(ECS), which coordinates membrane receptor activation with dynamic intracellular signaling to regulate homeostasis across neural, immune, and metabolic networks [163, 164]. The rationale for dual-targeting arises from bidirectional crosstalk between CB_1/CB_2 receptors and kinase pathways (e.g., MAPK, PI3K/Akt, AMPK, GSK3β), where cannabinoid receptors modulate kinase activity and, conversely, kinases regulate receptor signaling via phosphorylation-dependent trafficking and desensitization. These interactions are highly context-dependent, influenced by receptor localization, ligand bias, and cell type [165]. Hybrid

compounds that co-modulate cannabinoid receptors and kinases hold promise in conditions involving concurrent ECS and kinase dysregulation. CB_2–GSK3β and CB_1–AMPK hybrids show potential in neurodegeneration and metabolic disease, respectively, offering synergistic effects and reduced liabilities compared to monotherapies. Key challenges include achieving balanced target affinity, CNS penetration, and oral bioavailability, while avoiding pharmacodynamic interference. Tissue-specific variability in ECS and kinase signaling further complicates optimization, underscoring the need for context-driven design.

Table 5: Representative Hybrid Dual-Target Compounds Modulating ECS and Kinase Pathways.

Hybrid Compound Example	Primary Targets	Mechanism of Action	Therapeutic Rationale	Development Status
CB1 antagonist–PI3K inhibitor (e.g., SR141716A–PI3K hybrid)	CB1 receptor + PI3K-Akt pathway	Blocks CB1 signaling and oncogenic PI3K survival pathways simultaneously	Target ECS–PI3K axis in cancers such as glioma and colorectal cancer	Preclinical; rationally designed hybrid analogs
CB2 agonist–FAK inhibitor	CB2 receptor + focal adhesion kinase (FAK)	Activates anti-inflammatory CB2 signaling while inhibiting FAK-driven metastasis	Suppress tumor-associated inflammation and migration in cancer models	Experimental; early in vitro and in vivo validation

4. Future directions and therapeutic outlook

ECS signaling is shaped by kinase activity within membrane microdomains that coordinate receptor localization, ligand availability, and intracellular transduction[166]. Context-dependent kinase inhibitors (CDKIs) exploit these spatial features to modulate ECS pathways with high precision, limiting off-target effects. Emerging degraders such as PROTACs and molecular glues offer selective, irreversible targeting of ECS-linked kinases—enabling sustained pathway suppression without direct receptor engagement. Dual-target ligands co-activating or inhibiting cannabinoid receptors and kinases (e.g., CB_2–PI3K or CB_1–MAPK) may deliver synergistic effects with improved pharmacodynamic control. AI-driven drug discovery and structural modeling accelerate identification of ECS-relevant kinase inhibitors with brain-penetrant profiles [167]. Concurrently, advanced delivery systems—lipid nanoparticles and BBB-activated prodrugs—enhance tissue specificity and therapeutic index [168, 169]. As ECS–kinase interactions vary by genetic, metabolic, and environmental context, kinase-targeted modulation offers a precision-based path forward. Tailoring interventions to patient-specific ECS–kinase profiles may redefine cannabinoid pharmacology through intracellular, mechanism-informed control [170].

5. Conclusion

Kinome-targeted strategies offer a mechanistically grounded alternative to conventional ECS pharmacology, shifting the focus from receptor activation to intracellular signaling control. Unlike direct cannabinoid receptor ligands, which are limited by psychoactivity and desensitization, kinase modulation enables selective ECS pathway regulation without engaging psychotropic mechanisms. Importantly, the psychotropic effects of CB_1 activation remain incompletely understood, and endogenous cannabinoids have not demonstrated the same

activity as phytocannabinoids—undermining the rationale for targeting these receptors therapeutically. In this context, the kinome provides a more rational entry point. *Proof-of-concept* studies using ATP-competitive inhibitors, allosteric modulators, PROTACs, and hybrid ligands show potential for ECS-related applications, leveraging clinically validated kinase platforms. As these strategies evolve, they may redefine cannabinoid-based therapy through enhanced precision, reduced liability, and broader translational feasibility.

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