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Review Article

Cannabinoid Receptor 1: Allosteric Modulation and its Therapeutic Potential

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ABSTRACT

T*he cannabinoid receptors and endocannabinoid system play a role in many physiological processes which makes the cannabinoid receptor 1 a good target for therapies to a wide range of pathologies such as addiction, obesity, pain, depression, anxiety, and neurodegenerative disorders. Despite all of the therapeutic potential of creating cannabinoid receptor specific drugs, development of such medications has been difficult due to psychoactive side effects that are linked to agonist and antagonist ligands. This review focuses on describing cannabinoid receptor 1, its therapeutic potential, and exploring the possibility of using allosteric modulator compounds as a way to maximize medicinal benefit while limiting psychoactive side effects.*

Keywords: C*annabinoid receptor 1; allosteric modulator; G protein coupled receptor; ligands.*

1. ABBREVIATIONS

GPCR - G protein coupled receptor CB1 - cannabinoid receptor1

CB2 - cannabinoid receptor 2 CNS - central nervous system THC - Δ^9-tetrahydrocannabinol AEA - anandamide

2-AG - 2-arachidonylglycerol DAGL - diacylglycerol lipase

NAPE - N-arachidonoyl phosphatidylethanolamine MAGL - monoacyglycerol lipase

FAAH - fatty acid amide hydrolase FDA – food and drug administration GDP - guanosine diphosphate

GTP - guanosine triphosphate Gi - G inhibitory subunit

Gs - G stimulatory subunit PKA - protein kinase A

cAMP - cyclic adenosine monophosphate PAM - positive allosteric modulator NAM - negative allosteric modulator SAM - silent allosteric modulator

NAL - neutral allosteric ligand

KB - equilibrium binding constant.

2. INTRODUCTION

The cannabinoid receptors are G protein coupled receptors (GPCRs). There are two cannabinoid receptors that facilitate downstream signaling, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). CB1 is the most abundantly expressed GPCR in the central nervous system (CNS), but is also expressed in many peripheral tissues at lower concentrations. The CB2 receptor is mainly expressed in peripheral tissues, with higher expression in immune cells and organs such as the spleen and tonsils.[1; 2]

The Cannabis Sativa plant has a long history of medicinal, industrial, and religious use with first accounts of its usage stretching back approximately 5000 years.[3] The first pharmacological studies using isolated cannabis extracts were performed in the 1940s and 1950s. These early studies revealed pharmacological effects such as appetite augmentation, analgesia, catalepsy, impaired cognition, and

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psychoactive effects. The main psychoactive component of cannabis, Δ9-tetrahydrocannabinol (THC) (Fig. 1), was first classified by Dr. Mechoulam in 1964.[4] In the 1980s Allyn Howlett's laboratory provided the first conclusive evidence for the existence of cannabinoid receptors. [5; 6]

Since the discovery of the cannabinoid receptors, many cannabinoid ligands have been identified and studied for their therapeutic potential. While CB1 agonists such as THC and synthetic analogues have shown strong therapeutic potential, the physiological intricacies of endocannabinoid system (ECS) signaling has presented significant challenges such as untoward side effects, predominantly psychoativity. CB1 inverse agonist have also been studied as therapies such as rimonabant (SR141716A) which is a CB1 inverse agonist aimed to treat obesity, but was associated with severe depression [7] (Fig. 1). To date, the majority of therapeutics developed have been designed as orthosteric ligands targeting the endogenous ligand-binding pocket of CB1. While targeting the orthosteric site of GPCRs has proven successful for many other receptors and diseases, this approach may not result in useful therapies specific to CB1 due to interlinked psychotropic side effects. In recent years, the concept of allosteric modulation has been explored to create therapies for GPCRs where orthosteric ligands have not proven useful.

1.1 Tissue **Distribution of the Cannabinoid Receptors:**

The CB1 receptor is considered the most abundant GPCR in mammalian brain and has been studied for its role in physiology of pain, memory, anxiety, depression, motor coordination, nausea, autonomic function, substance abuse disorders and neurodegenerative disorders.[8; 9] While CB1 receptors are highly localized in central nervous system, the CB1 receptor is also expressed in peripheral tissues such as digestive, reproductive, and cardiovascular systems.[10; 11] Electron microscopy analyses have shown that CB1 receptors are predominantly located on presynaptic terminals of neurons, but there has also been evidence of CB1 receptors on postsynaptic terminals and glia.[12; 13] Within the CNS, CB1 receptors are chiefly expressed in the hippocampus, putamen, caudate, globus pallidus, and accumbens nucleus.[14] These areas of the central nervous system are associated with motor coordination, mood, sensation, memory, autonomic function and cognition. There is little expression of CB1 in the pons and medulla oblongata of the brain stem, which are areas responsible for respiratory and cardiovascular control. The lack of CB1 receptors in the brain stem is believed to be the reason there are no recorded instances of overdose from phytocannabinoids such as THC. The location of CB1 expression in the CNS can be correlated with the many effects attributed to cannabinoids. There is evidence that there is diminished CB1 expression and binding in neurodegenerative diseases, including Parkinson's and Huntington's disease.[15; 16] CB1 activation and hyperactivity is correlated with increased food intake, lipid metabolism, fat accumulation, and glucose metabolism.[14] Stimulation of CB1 receptors in the hypothalamus results in modulation of neuropeptides which play a role in regulating energetic homeostasis, lipogenesis in visceral tissues, and food intake. There is also evidence that activation of CB1 in the accumbens nucleus triggers reward pathways leading to motivation to consume food, but also has been associated with drug seeking behaviors.[17] There is high expression of CB1 receptors in the periaqueductal gray area in the dorsal horn of the spinal cord which is correlated with pain modulation of CB1 receptors. CB1 activation has an analgesic effect, which may be useful in development of less addictive and dangerous pain medications.

CB2 receptors are expressed at low levels in the central nervous system, but much higher levels in peripheral tissues. CB2 receptors are expressed on immune cells and in immune system tissues where they are believed to play a role in immune cell modulation. CB2 receptors are found at high concentration in organs such as the tonsils, spleen, thymus, and bone.[18; 19] Specific cells have been identified to have high CB2 expression including CD4+ and CD8+ T cells, B cells, monocytes, killer cells, and neutrophils.[20; 21] While CB2 is considered as the peripheral cannabinoid receptor, there is evidence that CB2 is also expressed in the brain at lower concentrations. Microglia are the resident macrophage within the brain and have been found to express CB2. Recent studies have demonstrated that CB2 modulation in the brain can result in microglia migration to damaged areas of the brain.[22; 21].

1.2 The Endocannabinoid System:

The endocannabinoid system is primarily composed of the CB1 and CB2 receptor subtypes, endogenous ligands specific to those receptors, and the enzymes involved in their synthesis, transport and metabolism.[23] There are two major endocannabinoid ligands, anandamide (AEA) (N-arachidonyl-ethanolamine) and 2-arachidonylglycerol (2-AG). AEA and 2-AG are unlike traditional neuromodulator compounds because they are produced on demand rather than being synthesized and stored in vesicles.[24] This characteristic of AEA and 2-AG makes the endocannabinoid system transient in nature. 2-AG is synthesized from the precursor lipid diacylglycerol which exist within cell membranes. Diacylglycerol is catalyzed via hydrolysis by diacylglycerol lipase (DAGL). AEA is synthesized by phospholipase enzymes from the precoursor N-arachidonoyl phosphatidylethanolamine (NAPE).[25] Endocannabinoids are produced at the postsynaptic neuronal terminal upon stimulation, released into the synaptic space where they interact with cannabinoid receptors on the presynaptic membrane. Endocannabinoids take advantage of a retrograde signaling mechanism which allows for modulation of neurotransmitter release from the presynaptic neuron. Recent evidence suggests that 2-AG and AEA bind some non CB1 and CB2 receptors such as GPR55. GPR55 has less than 20 percent sequence homology to that of CB1 and CB2 and is considered by some a third cannabinoid receptor, but more research is needed.[26] Endocannabinoids have a relatively short half-life and are degraded by monoacyglycerol lipase

(MAGL) and fatty acid amide hydrolase (FAAH). The CB1 receptor demonstrates basal activity in the absence of cannabinoid agonists and has also been found to be readily internalized without direct stimulation.[27] While CB1 receptors seem to demonstrate basal activity there is debate on whether the cannabinoid receptors should be considered to have constitutive activity. It has been difficult for researchers to design experiments where no endocannabinoids are present because they are constantly synthesized and degraded from lipid membranes making it difficult to distinguish constitutive activity from endogenous agonist tone.[28] Inverse agonists such as SR141716A have shown the ability to attenuate G-protein coupling and downstream ERK phosphorylation.[29] Better inhibitors of endocannabinoid synthesis need to be developed in order to distinguish between endogenous agonist tone and constitutive activity.

1.3 CB1 Signal Transduction:

When the CB1 receptor becomes activated or bound to an extracellular ligand, a shift in the receptor state occurs which results in triggering of intracellular signaling cascades. The CB1 receptor primarily signals through coupling and activation of G-proteins, hence its classification as a GPCR. When the CB1 receptor is activated a heterotrimeric G-protein binds the intracellular potion of the receptor. A guanosine-nucleotide exchange occurs where guanosine diphosphate (GDP) is exchanged for guanosine triphosphate (GTP) which results in dissociation of the heterotrimeric G-protein complex into α and βγ subunits. Both the α and βγ subunits have potential to facilitate downstream signaling. Different categories of G-proteins exist including Gi (G inhibitory) and Gs (G stimulatory). The CB1 receptors binds preferentially to Gi proteins which have been identified to directly inhibit adenylate cyclase. CB1 activation has been shown to be pertussis-toxin sensitive suggesting that CB1 interacts with Gi proteins because pertussis-toxin prevents Gi proteins from coupling to GPCRs.[30] Adenylate cyclase plays a role in converting ATP into cAMP (cyclic adenosine monophosphate), therefore activation of Gi proteins results in inhibition of adenylate cyclase and decreased cAMP levels. cAMP functions as a downstream signaling molecule which activates kinases such as protein kinase A (PKA). Activated PKA results in phosphorylation of kinase cascades. Downstream kinases such as ERK become phosphorylated and translocated to the nucleus where they interact with transcription factors resulting in altered gene expression. There is also evidence that activation of CB1 and Gi proteins causes inhibition of L-type and N-type calcium channels.[31; 32] Evidence suggests that cannabinoids suppress neuron excitability by inhibition of neurotransmitter release as a result of calcium channel inhibition in the presynaptic terminal. While CB1 is considered to mainly bind Gi proteins, studies have shown that specific cell lines in culture have different G-protein profiles and that CB1 has the potential to bind to different G-proteins. This variation in G- protein coupling has also been explained by the ligand dependence where two different ligands for CB1 result in different G-protein coupling. For example, HEK293 cells transfected with a CB1 receptor plasmid and treated with the CB1 agonist WIN55212-2 resulted in Gq mediated calcium signaling while a different agonist CP55,940 resulted the usual Gi coupling.[33] β-arrestin proteins interact with the CB1 receptor facilitating both signaling and receptor internalization. The β-arrestin-2 isoform is associated with internalization of an activated CB1 receptor, but there is evidence that β-arrestin-1 can facilitate signaling in a β-arrestin-1 dependent manner.[34] β-arrestin 2 knockout mice showed increased antinociceptive responses to THC as well as decreased tolerance while β-arrestin 1 knockout mice showed a reduced sensitivity of downstream signaling upon application of full agonist CP55,940.[35; 36] The CB1 receptor has been shown to interact with other intracellular proteins including GPCR-associated sorting protein (GASP-1), adaptor protein FAN, and adaptor protein AP-3 which play roles in trafficking and signaling. [37-39].

1.4 Allosteric Modulation of GPCRS:

Allosteric modulators are ligands that bind the allosteric site which is topographically separate from the orthosteric binding site on a GPCR. Allosteric modulators are categorized into four classes based on how they modulate orthosteric ligand affinity or efficacy. First, positive allosteric modulators (PAMs) bind and activate the receptor potentiating orthosteric agonist affinity or efficacy (Fig. 2). Second, negative allosteric modulators (NAMs) bind and inactivate the receptor attenuating orthosteric agonist affinity or efficacy. Third, ago-allosteric modulators or silent allosteric modulators (SAM) bind the receptor and modulate receptor signaling independent of orthosteric ligand binding. Fourth, neutral allosteric ligands (NALs) bind the allosteric site of the receptor but do not modulate receptor function.[40] Allosteric modulators often exhibit probe dependence in which the same allosteric compound for a receptor may function differently dependent on the orthosteric ligand. For example, some allosteric modulators that exhibit probe dependence can exhibit NAM like characteristics when accompanied by one ligand, and can exhibit PAM like characteristics with a different ligand. [41]

Allosteric modulators present possible advantages over the use of orthosteric compounds because allosteric drugs display more subtype specificity since the orthosteric site on GPCRs tend to be more conserved among receptor subtypes. This is due to high evolutionary pressure to maintain endogenous ligand binding, while allosteric sites show more subtype specificity in the absence of that evolutionary pressure.[42] In recent years, pharmacological studies have shown that GPCRs have the tendency to exhibit functional selectivity (Fig. 3). Functional selectivity is a ligands ability to stabilize a receptor in a conformation which preferentially binds to a specific subset of intracellular signaling molecules and selectively modulates certain response pathways. [43; 44] For example,

CB1 ligands CP55,940, WIN55212-2, HU210, anandamide, and 2-arachidonoylglycerol are thought to bind similarly to orthosteric binding pocket on CB1, but may provoke preferential interactions with varying subtypes of G-proteins (i.e., Go, Gi, Gs, and Gq/11), resulting in different efficacies and ligand-dependent functional selectivity.[45; 46] Allosteric compounds have the potential to maintain temporal fidelity of endogenous signaling molecules because some allosteric modulators (non ago-allosteric) will only function in the presence of the endogenous ligand. This is key because these allosteric compounds can supplement native signaling rather than displacing the endogenous ligands. Moreover, not all receptors will be impacted, but rather only modulate signaling of the receptors bound to endogenous ligand. Allosteric ligands may also reduce potential for tolerance and overdose because binding of an allosteric compound may not trigger internalization or desensitization in the way orthosteric agonists often do.[42; 47] Lastly, allosteric compounds present the opportunity to develop therapeutics for receptors where targeting the orthosteric site has not resulted in therapeutically useful drugs.[47].

1.5 Detection and Quantification of Allosteric Compounds

Allosteric modulators can be detected and quantified using radiolabeled binding assays. Equilibrium binding assays can be utilized to identify two principal parameters for understanding allosteric properties including the equilibrium binding constant (KB) which defines the affinity of an allosteric modulator for its receptor in the presence of an orthosteric compound, and the cooperativity factor alpha (α) which defines the impact the allosteric modulator and orthosteric compound have on one another when occupying the same receptor. In the presence of an agonist, an $\alpha > 1$ indicates a positive cooperativity while an $\alpha < 1$ indicates a negative cooperativity and an $\alpha = 1$ denotes no allosteric modulation. The parameters above can be calculated based on the allosteric ternary complex model.[48;49]

$$Y= [A]/[[A]+(KA (1+[B]/KB)/(1+\alpha [B]/KB))]$$

In the allosteric ternary complex model Y represents a fractional specific binding; KB and KA are the equilibrium dissociation constants of the allosteric and orthosteric ligands respectively; [B] and [A] are the concentrations of the allosteric and orthosteric ligands respectively, and α is the cooperativity factor. A second method to detect allosteric modulation is applying kinetic binding assays to determine the effect of allosteric compounds on the dissociation or association of orthosteric ligands.[50] NAMs decrease the association kinetics or increase the dissociation kinetics of the orthosteric agonists, while PAMs decrease the dissociation kinetics or increase the association kinetics of orthosteric agonists.

Functional assays such as cAMP assays can be applied to allosteric interactions. Functional assays detect downstream effects a compound has on the signaling facilitated by a bound receptor. For example, AEA is an activating agonist for the CB1 receptor which decreases cAMP levels by inhibiting forskolin-stimulated cAMP production, when AEA was co-administered with the experimental allosteric modulator ZCZ011, cAMP levels were further inhibited suggesting PAM characteristics of ZCZ011.[51]

1.6 Allosteric Modulation of CB1

The development of therapeutically useful drugs that target the CB1 receptor has been difficult due to unwanted side effects. CB1 agonists are often associated with psychoactive effects while antagonists and inverse agonists are associated with depression and anxiety. Traditional ligands of the CB1 receptor have demonstrated great therapeutic potential, but separating the side effects from the medicinal properties may require fine tuning of the receptor. It is hypothesized that the development of allosteric modulators targeting CB1 may provide the fine tuning necessary.

To date, approximately nine compound classes of CB1 allosteric modulators have been identified, some of which include the synthetic compounds ORG27569, PSNCBAM-1, GAT211, and ZCZ011 [52] (Fig. 4). These allosteric modulators and some derivatives show therapeutic potential. The exact allosteric binding sites in which these compounds interact with CB1 are still under investigation, with many proposed sites.[53; 54] ORG2756 was among the first CB1 allosteric modulators characterized. ORG2756 was found to increase binding affinity of CB1 agonist CP55,940 and was found to decrease the affinity of CB1 inverse agonist SR141761A. These findings suggest that ORG2756 functions as a PAM.[49; 55; 56] Paradoxically, GTPγS binding assays revealed that ORG2756 decreased CP55,940 induced G-protein coupling but data suggests that signaling may shift towards a β-arrestin dependent pathway. ORG27569 was also found to exhibit probe dependence.[49; 57; 55; 58] Kendall and colleagues demonstrated that upon treatment of HEK293 cells with both CP55,940 and ORG27569, there was a significant acceleration in the internalization of the CB1 T210A receptor. Increased receptor internalization began at 10 min and evened out by 20 min, compared to the internalization upon treatment with CP55,940 alone which leveled out at 40 min.[55]

ZCZ011 and GAT211 are two recently classified PAMs with very different structure than ORG2756 and exist as a racemic mixture of R and S enantiomers due to a chiral center at the C10 position (Fig 4). These compounds have demonstrated potential pharmacological effects in the management of neuropathic pain and glaucoma.[59; 60] ZCZ011 enhanced AEA stimulated β-arrestin recruitment, ERK phosphorylation, and GTPγS binding.[51] In this study, ZCZ011 showed evidence of reducing neuropathic pain in mice with little evidence of psychoactive effects.[51] A 2019 study by Trexler and colleagues revealed that ZCZ011 may attenuate THC withdrawal symptoms and may also counteract NSAID-induced gastric inflammation in mice.[61] In a different study,

the chemically similar compound GAT211 was found to suppress allodynia in wild-type mice, but not CB1 knockout mice. This same study also suggests that GAT211 may suppress pathological pain without increasing dependence or tolerance in mice.[62] While early studies into CB1 PAMs show some promise as safe and effective analgesics, further investigation into allosteric modulators of the CB1 receptor is necessary in order to develop useful therapeutic drugs.

1.7 CB1 Therapeutic Potential

The cannabis sativa plant has a history of medicinal use dating back thousands of years, yet was outlawed in the United States in 1937 due to its psychoactive side effects. In the U.S. today, cannabis containing THC is considered a schedule one drug, which states that the plant has no accepted medical use and a high potential for abuse. Nonetheless, medical marijuana has been approved in 33 U.S. states. Medical marijuana has been prescribed to manage pain associated with peripheral neuropathy, multiple sclerosis, and cancer.[63-65] Other than medical marijuana, there is currently a few food and drug administration (FDA) approved cannabinoid ligand drugs including Nabilone (Cesamet), Sativex, and Dronabinol (Marinol & Syndros). These drugs are cannabis-based therapeutics which contain a form of THC as the main active ingredient. Nabilone and Dronabinol is used to treat nausea associated with cancer and AIDS, while Sativex is used for treatment of multiple sclerosis induced pain and decreased plasticity.[66; 67] Epidiolex is a cannabidiol medication, which can be prescribed for treatment of two rare forms of childhood epilepsy, Lennox-Gastaut syndrome and Dravet syndrome.[68]

The CB1 receptor has been targeted to create anti-obesity drugs because it is known to play a role in energy balance and food consumption. Activation of CB1 receptors promotes the expression of fatty acid synthase in both the hypothalamus and hepatocytes, while also increasing activity of lipoprotein lipase in adipocytes.[69; 70] CB1 inverse agonists and antagonists have been the focus of studies for their ability to Fight obesity. Preclinical studies demonstrated the effectiveness of these drugs in decreasing food consumption and increasing weight loss.[71] While these drugs were found to work as anti-obesity medications, the medicinal effects were accompanied by side effects such as severe depression and anxiety. One CB1 inverse agonist, named rimonabant, was on the clinical market in Europe, but was quickly removed because of these side effects.[7]

Another area of potential CB1 therapeutics exists in addiction disorders. Activation of the CB1 receptor has been associated with reward behaviors observed in addiction. Solinas and colleagues showed that administration of the CB1 antagonist SR141716A could decrease self-administration of heroin in mice.[72] A different study by Economidou demonstrated that SR141716A could decrease alcohol consumption in mice.[73] While CB1 antagonists and inverse agonists show potential in decreasing addictive behavior, no one has been able to separate the medicinal effect from the mood depressing side effects.

The CB1 receptor plays a role in pain sensation. The CB1 receptor is densely expressed in areas of the brain involved in modulation and perception of pain such as the amygdala and thalamus. It is well known that CB1 receptor agonists have anti-hyperalgesic and antinociceptive effects at the central and peripheral nervous system. This modulation of pain sensation has been demonstrated in acute and chronic pain models.[74; 75] Activation of the CB1 receptor decreases nociception by regulating neuronal activity and attenuating synaptic transmission.[76] CB1 agonists may be useful therapeutics in treating neuropathic pain due to their ability to attenuate false pain impulses from abnormally functioning peripheral pain receptors. The antinociceptive effects of CB1 agonists may not be totally due to interactions with the cannabinoid receptors. There is evidence that some cannabinoid receptor agonists interact with other GPCRs such as the type one vanilloid receptor.[77; 76] The major drawback of applying CB1 agonists as pain medicines is the inability to separate the psychoactive side effects associated with CB1 activation.

3. CONCLUSION

In conclusion, CB1 and the endocannabinoid system play a fundamental role in many physiological processes that make the CB1 receptor a good target for therapies to a wide range of pathologies such as addiction, obesity, pain, depression, anxiety, and neurodegenerative disorders.[2; 78; 79] While the CB1 receptor presents tremendous therapeutic value, previous attempts at producing CB1 specific drugs have often resulted in non-therapeutic psychoactive side effects which accompany the useful therapeutic effects.

In the past two decades researchers have begun investigating allosteric modulation as a way to separate the therapeutic effects of the CB1 receptor from the psychoactive component. In the past decade multiple CB1 allosteric modulators have been identified and studied, with recent compounds such as GAT211 and ZCZ011 showing therapeutic potential with limited psychoactive effect and less evidence of tolerance or dependence in mice.[51; 62] While allosteric compounds such as GAT211 and ZCZ011 show promising potential, further investigation into these compounds and the development of better allosteric modulators for the CB1 receptor is required to arrive at a clinically relevant CB1 allosteric drug.

4. ACKNOWLEDGMENT

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5. CONFLICT OF INTEREST

All authors declare they have no conflict of interest to disclose.

6. FIGURES

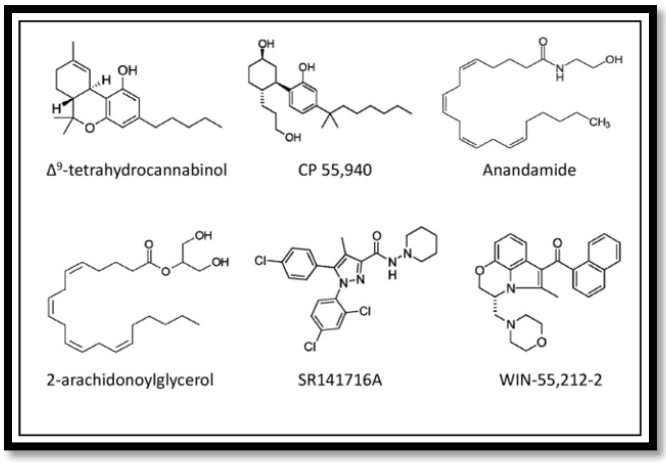

Fig. 1. Cannabinoid receptor ligands. Structures of select CB1 ligands.

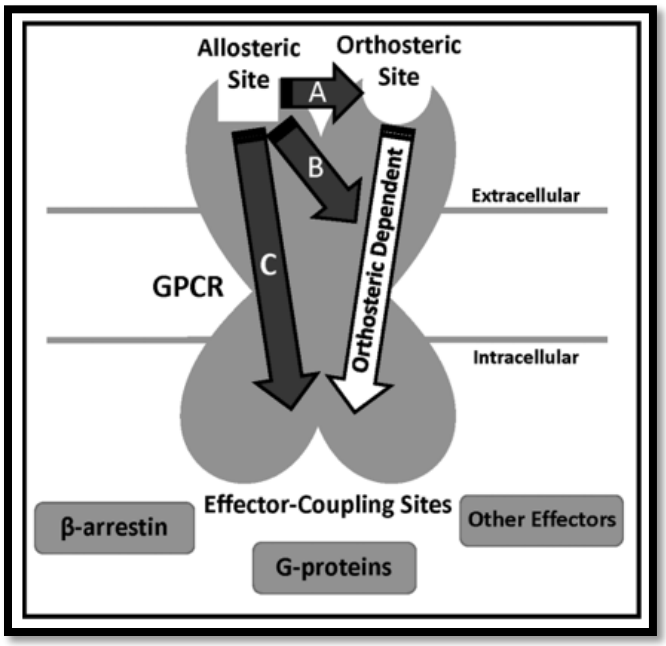

Fig. 2. Representation of GPCR allosteric modulation. Allosteric modulators bind a topographically distinct location from orthosteric ligands. Binding of an allosteric modulator may alter orthosteric ligand binding affinity (arrow A), modulate orthosteric ligand efficacy (arrow B), or alter effector coupling (arrow C). White arrow represents orthosteric dependent efficacy.

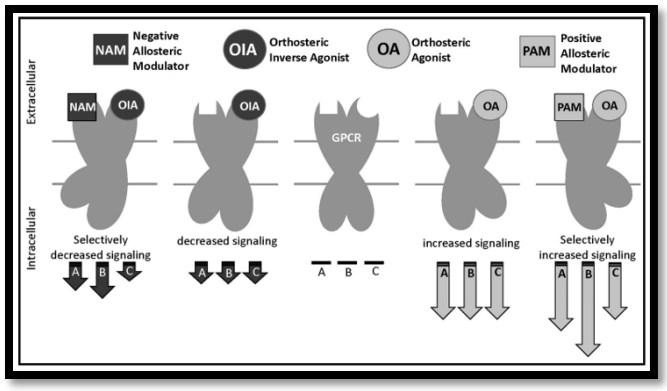

Fig. 3. Schematic representation of GPCR allosteric modulation and functional selectivity. Binding of an orthosteric agonist or inverse agonist results in global increases or decreases of possible intracellular signaling pathways A, B, and C. Binding of an orthosteric ligand in the presence of an allosteric modulator results in selective increases or decreases in signaling pathways A, B, and C in a manner unachievable with orthosteric ligands alone. Allosteric modulation of CB1 may increase therapeutic effects while lowering side effects by selectively modulating signaling pathways.

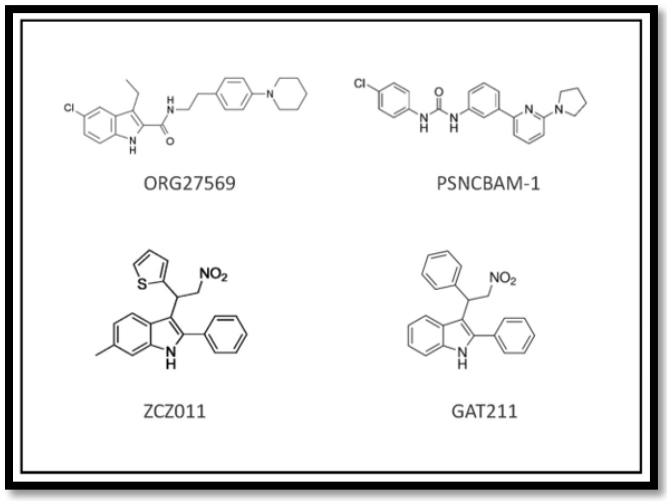

Fig. 4. CB1 allosteric modulators. Chemical structure of select CB1 allosteric modulators.

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