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CB₂: Therapeutic target-in-waiting

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Abstract

CB₂ cannabinoid receptor agonists hold promise as a new class of therapeutics for indications as diverse as pain, neuroinflammation, immune suppression and osteoporosis. These potential indications are supported by strong preliminary data from multiple investigators using diverse preclinical models. However, clinical trials for CB₂ agonists, when they have been reported have generally been disappointing. This review considers possible explanations for the mismatch between promising preclinical data and disappointing clinical data. We propose that a more careful consideration of CB₂ receptor pharmacology may help move CB₂ agonists from “promising” to “effective” therapeutics.

Keywords

cannabinoid; functional selectivity; drug development; tolerance

1. Introduction

Cannabis derivatives have a long and storied history of medicinal use. This use has been put on a firmer scientific footing with the identification of many cannabis constituents (cannabinoids) and the elucidation of an endogenous cannabinoid signaling system. This latter system is comprised of cannabinoid receptors, the endogenous cannabinoids (endocannabinoids) that engage those receptors, and the enzymes that synthesize and degrade endocannabinoids (Howlett et al., 2002). The long history of medicinal cannabis use, plus the richness of the endogenous cannabinoid signaling system offers many opportunities for the therapeutic applications of cannabinoids and drugs that modulate the endocannabinoid system. Unfortunately, many of these opportunities have not been realized. This review will focus on why this may be the case for CB₂ cannabinoid receptors.

The primary receptors of the endocannabinoid system are the CB₁ and CB₂ cannabinoid receptors. Of these, the CB₁ receptor is the best studied. These receptors mediate the psychoactivity of cannabis, as well as the antiemetic and analgesic actions of Δ₉tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. In addition, CB₁ receptors regulate several metabolic processes, and when engaged by inverse

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agonists such as rimonabant lead to weight loss and an improvement in metabolic parameters (Despres et al. , 2005).

In contrast to CB₁ receptors, the physiological roles of CB₂ receptors are considerably less well understood. For example, in contrast to the myriad effects of CB₁ receptor deletion, the reported consequences of knocking out CB₂ receptors are rather subtle, primarily involving modest perturbations in the immune system (Buckley, 2008, Buckley et al. , 2000). Most of what we know about CB₂ receptor function comes from pharmacological studies using CB₂ receptor agonists and antagonists. These studies suffer from the usual caveats of pharmacological studies—the possible confounds of inadequate drug specificity and selectivity. Nonetheless, there is now considerable evidence for a CB₂ role in several pathologies lacking satisfactory treatments. The pathological processes for which the evidence of CB₂ involvement is strongest, and also those that are perhaps the most promising in terms of drug development are neuroinflammation and pain (Cheng and Hitchcock, 2007, Guindon and Hohmann, 2008). However, therapeutic opportunities based on the manipulation of CB₂ receptors exist for many other pathological conditions, including systemic inflammation, osteoporosis, cancer, transplantation biology, several CNS disorders including drug addiction and anxiety, and liver disease, to name a few (Bab et al. , 2009, Karsak et al. , 2007, Mallat and Lotersztajn, 2010, Nagarkatti et al. , 2010, Patel et al. , 2010, Xi et al. , 2011).

2 CB₂ receptors and their signaling

2.1 CB₂ receptor distribution

CB₂ receptors were first conclusively identified and cloned from the HL60 promyelocytic leukemic cell line (Munro et al. , 1993). Their identification in several leukemic cell lines and their presence in many circulating immune cells and the spleen (Galiegue et al. , 1995), with lesser levels elsewhere in the body focused initial attention on this receptor as a mediator of various immune effects of cannabinoids. This led to the embrace of the overly simplistic generalization of a brain/periphery dichotomy, with CB₁ receptors responsible for the CNS effects of cannabinoids and CB₂ receptors contributing to their immune actions. Subsequent studies have clearly demonstrated that this “black and white” delineation is incorrect, with CB₁ expression in immune cells and CB₂ expression in CNS and other tissues.

Despite the expenditure of considerable scientific capital there remains much confusion as to the exact disposition of CB₂ receptors (Atwood and Mackie, 2010). This is in part simply the ‘nature of the beast’ – GPCRs are generally difficult to immunolocalize (Thomas, 2009). For several reasons these proteins do not lend themselves to the development of specific antibodies. This limited immunogenicity, coupled with the observation that most GPCR’s are expressed at low levels, makes their detection problematic. Ironically, the unusually high expression levels of CB₁ receptors and their immunogenicity has contributed to the confusion surrounding CB₂. Thus, whereas multiple highly effective CB₁ receptor antibodies have been generated, and used to efficiently map CB₁ receptor expression throughout the brain (Egertova and Elphick, 2000, Tsou et al. , 1998), CB₂ staining has proven fitful. The example of CB₁ is instructive since most immunocytochemical studies of CB₁ receptors only label neurons expressing the highest levels of CB₁ receptors. For example, even though there is clear functional and molecular data for expression of CB₁ receptors on the hippocampal Schaeffer collaterals, these receptors are difficult to detect at the light microscopic level (Hajos et al. , 2000). Only the development of mice lacking CB₁ receptors in GABAergic neurons, which reduces hippocampal CB₁ levels by ~90% (Monory et al. , 2006), conclusively settled the controversy regarding CB₁ expression at these and other glutamatergic synapses.

For scientists accustomed to working in the cannabinoid field, there was the implicit assumption that since CB₁ receptors were easy to detect using immunocytochemical techniques, the same would hold for CB₂ receptors. This has proven not to be the situation. While it was relatively simple to raise antibodies that could detect CB₂ receptors in transfected cells, successful application of these antibodies to study natively expressed CB₂ receptors in the CNS has remained elusive (Atwood and Mackie, 2010). In part, this difficulty may be explained by the relatively low levels of CB₂ receptor expression in the brain. At the transcript level, CB₂ receptors are only about 5% as abundant as CB₁ receptors (Onaivi et al. , 2008), with a significant portion of this CB₂ mRNA actually derived from leukocytes trapped in the cerebral vasculature. Further complicating an assessment of CB₂ levels and distribution is the fact that CB₂ levels are highly inducible. For example, in an experimental allergic encephalitis model, spinal cord CB₂ mRNA can increase almost 100-fold over an interval of several days (Maresz et al. , 2005). While this might be attractive from a therapeutic perspective, as CB₂ will be upregulated in areas of tissue pathology where its activation might be beneficial, it also complicates evaluation of receptor distribution. Thus, an examination of CB₂ receptor expression and distribution requires especially careful consideration of the conditions of that expression.

Despite these limitations, the following findings about CB₂ receptor distribution are generally well accepted in the field: (1) CB₂ receptors are expressed on many macrophage-derived cells. These include microglia, many circulating macrophages, osteocytes and osteoclasts, dendritic cells, and hepatic Kupffer cells. (2) CB₂ expression is subject to tight regulation and is highly induced following inflammation or tissue injury. (3) CB₂ receptors potentially modulate immune responses, both positively and negatively. (4) CB₂ may be expressed on some neurons, particularly following injury. This may follow injury to either the neuron or to the tissue surrounding the neuron (especially in the periphery - a more in-depth discussion of these issues can be found in a recent review addressing CB₂ expression in the brain (Atwood and Mackie, 2010)).

2.2 CB₂ receptor signaling pathways

CB₂ receptors are class A GPCR's. As such they have a relatively short extracellular domain and bind their ligand in a fashion that involves several transmembrane domains. CB₂ receptors predominantly couple to Gi and Go G proteins (Howlett, Barth, 2002). Thus, activation of CB₂ receptors reliably leads to inhibition of adenylyl cyclase and stimulation of several mitogen-activated protein (MAP) kinases. Whether or not CB₂ modulates ion channels has been controversial. An early report suggested they did not modulate either inwardly rectifying potassium channels or high voltage-activated calcium channels when expressed in AtT20 cells (Felder et al. , 1995). More recent work suggests that they do modulate these channels and that the earlier results were the result of marked functional selectivity (see below) on the part of the ligands used in this study. CB₂ receptors activate additional signaling pathways under certain conditions including activation of phospholipase C leading to the release of calcium from intracellular stores (Shoemaker et al. , 2005), regulation of small G proteins (such as Rho, Rac, and cdc42) (Kurihara et al. , 2006), and stimulation of signaling via the phosphatidylinositol 3 kinase (PI3K)/Akt pathway, leading to JNK activation (Viscomi et al. , 2009).

2.3 Regulation of CB₂ receptors expression and function

As mentioned above, CB₂ receptor expression may be strongly induced during pathological states. This may be therapeutically beneficial; if CB₂ receptors are strongly upregulated in a particular diseased tissue, it may be possible to selectively activate receptors in those tissues (e.g., by taking advantage of the pharmacological concept of "spare receptors" (Nickerson, 1956)), decreasing the possibility of deleterious side effects. This stands in marked contrast

to CB₁ receptors, whose widespread distribution and involvement in multiple physiological processes have complicated the development of CB₁-based therapies, whether via an agonist or an antagonist (Lazary et al. , 2011, Moreira and Wotjak, 2010, Seely et al. , 2011).) Our understanding of the processes underlying regulation of CB₂ expression in various pathologies is at an immature state as there have been only a few studies addressing this (e.g., (Liu et al. , 2009, Sherwood et al. , 2009)) and none that have systematically analyzed the CB₂ promoter. This is an area in need of additional research.

GPCR's are regulated at many levels. Relevant to this review and for the development of CB₂ -active drugs as therapeutics, are the effects of sustained CB₂ receptor activation. Although there are variations among GPCR's and between different tissues the general pattern for receptor regulation is as follows (Gainetdinov et al. , 2004): Once a GPCR has been activated by a ligand its signaling is attenuated by desensitization processes, typically followed by receptor internalization. Desensitization generally involves G protein receptor kinase-mediated phosphorylation of multiple serine or threonine residues of the GPCR, followed by binding of a beta-arrestin (arrestin2 or arrestin3), which sterically limits further interactions between the alpha subunit of the heterotrimeric G protein with the receptor. Additional protein components are then recruited towards the phosphorylated receptor/arrestin, thereby producing a protein complex. This large complex localizes to specific plasma membrane domains (often clathrin-coated pits or caveolae), depending on the nature of the GPCR and cell. Receptor internalization typically occurs from these specialized domains. Different fates await the internalized receptor. It may be trafficked to endosomes where the GRK-phosphorylated receptors are dephosphorylated. The resensitized receptor can then be re-inserted into the plasma membrane, where it is available for signaling the next time agonist is present. Alternatively, the GPCR may be internalized and directed towards lysosomes, where it is degraded, effectively down regulating signaling by that receptor in the cell. In recent years it has become clear that arrestin-bound, internalized receptors are still capable of signaling to effectors that differ from those present on the plasma membrane. This is often through the recruitment of additional signaling pathways, for example ERK and tyrosine kinases (e.g., src kinase) (Luttrell, 2005, Pierce and Lefkowitz, 2001).

Surprisingly little is known about the processes involved as the CB₂ receptor adapts to chronic activation. What we do know comes primarily from over expression of CB₂ in cell lines. While expression systems offer useful information and are necessary for many mechanistic studies, it needs to be kept in mind that the expression levels attained in these systems typically vastly exceed the levels found when CB₂ is expressed in vivo. For this and other reasons, the pathways engaged in these systems may vary from those utilized in vivo and this caveat must be considered when interpreting results from expression systems.

The first insights into CB₂ receptor regulation during chronic receptor activation came about quite fortuitously. These studies used an antibody that was made against a C-terminal domain of human CB₂. When characterizing this antibody in CHO cells expressing CB₂ it turned out that the dominant epitope recognized by the antibody was against the non-phosphorylated form of the corresponding receptor domain. Thus, this antibody serendipitously proved to be a useful tool to examine phosphorylation state of the CB₂ receptor. In these studies it was found that CP55,940, a cannabinoid receptor agonist, stimulated phosphorylation of CB₂ serine 352 and this phosphorylation was persistent (>8 hours). The phosphorylation was reversed by the CB₂ receptor inverse agonist, SR144258, in a process involving a protein phosphatase (Bouaboula et al. , 1999). Since CB₂ is internalized by CP55,940 treatment, these results suggested that the inverse agonist (1) displaced CP55,940 from the internalized receptor and/or (2) induced a conformational change in CB₂ that permitted dephosphorylation of serine 352. To date, this is the only

known GRK phosphorylation site of CB₂, although by inference from other GPCR's there are likely to be additional CB₂ GRK phosphorylation sites.

Several studies have investigated CB₂ receptor internalization (Bouaboula, Dussosoy, 1999, Carrier et al. , 2004, Grimsey et al. , 2011). These studies suggest that certain agonists stimulate CB₂ receptor internalization and that there is a disconnect between CB₂ agonists that stimulate its internalization and those that stimulate other CB₂ signaling pathways. The reversibility of CB₂ internalization suggests that it is transient, at least in CHO and HEK293 cells, identifying CB₂ as belonging to the class of recycling GPCR's. The role of CB₂ receptor internalization in cells constitutively expressing CB₂ receptors remains to be thoroughly investigated.

Almost all of what we know about CB₂ receptor regulation during chronic activation comes from studies in expression systems. As briefly mentioned above, there are significant challenges in extrapolating these results to *in vivo* conditions. Most drug development in the CB₂ field has focused on the development of CB₂ receptor agonists. However, there are few published data on the consequences of long term CB₂ agonist administration on (pre)clinical efficacy, particularly in pain, which is perhaps the most promising indication for CB₂ agonists and where the reported clinical trials have been focused. Thus, there is an urgent need to better understand the effects of chronic CB₂ activation and possible tolerance and receptor down regulation in the *in vivo* preclinical models.

CB₂ receptors show significant divergence between species. Overall the human CB₂ and mouse CB₂ receptors are 82 % identical. However, the amino terminus and carboxy terminus are more divergent, only showing 56% and 57% similarity, respectively (Brown et al. , 2002). Particularly striking are the differences in the distal carboxy terminus of CB₂. It has been suggested that these differences arise from an instability in the gene, predisposing it to chromosomal translocation (Brown, Wager-Miller, 2002). Since the distal carboxy terminus is important in many aspects of GPCR regulation, the considerable intra-species differences in this region of the CB₂ receptor suggests that CB₂ receptor regulation may also significantly differ across species. Until these potential regulatory differences are better understood, their potential presence mandates caution in extrapolating mechanisms of CB₂ regulation determined in one species to another species.

2.3 CB₂ receptor pharmacology

Because of the therapeutic potential of CB₂ ligands, a large number of structurally distinct CB₂ agonists and antagonists have been synthesized and characterized. Due to space limitations that literature won't be reviewed here. Interested readers should refer to several recent studies (Ashton et al. , 2008, Beltramo, 2009, Guindon and Hohmann, 2008, Manera et al. , 2008, Marriott and Huffman, 2008, Thakur et al. , 2009). In this section we will focus on general caveats when interpreting the literature and discuss some general pharmacological concepts that are especially relevant when considering pharmacological studies employing CB₂ ligands.

2.3.1 Specificity and selectivity—Lipid signaling systems are notoriously promiscuous—all lipid receptors, including CB₂, bind multiple, structurally diverse endogenous ligands. Conversely, very few, if any, truly selective CB₂ ligands exist. Furthermore, it is difficult to exclude off target effects as it is impossible to screen any particular agonist against all possible GPCR's (not to mention other targets, such as TRP channels and nuclear receptors such as the PPAR family). Furthermore, the considerably higher density of CB₁ receptors compared to CB₂ receptors will favor signaling by CB₁ receptors activated by CB₂ ligands, even though the fractional occupation of the CB₁ receptor may be quite low. For all of these reasons, the identification of a "CB₂ -selective" or "CB₂ -specific" ligand is a highly

operational definition, quite relative, and subsequent to revision as new data become available. Thus, multiple approaches must be employed before it is safe to conclude that a particular response is mediated by a ligand acting via CB₂ receptors. For example, the concurrent use of CB₂ KO mice (or CB₂ receptor knockdown in non-murine animals), structurally distinct CB₂ agonists, and structurally distinct CB₂ antagonists collectively serve as a much stronger test of CB₂ involvement compared to the use of a single CB₂ agonist. Rigorously applying these criteria to studies investigating the involvement of CB₂ will help clearly establish the physiological and pathophysiological role(s) of this signaling system and resolve some discrepancies in the literature (Atwood and Mackie, 2010).

2.3.2 Efficacy, inverse agonism and protean agonism—An important tenet of conventional receptor pharmacology is that receptor activation is a graded response, with different agonists capable of individual levels of maximal receptor activation. These differences in maximal activation are referred to as intrinsic efficacy. Thus, compounds of higher intrinsic efficacy are capable of stimulating greater receptor signaling than those of lower intrinsic efficacy. However, the cellular readout of intrinsic efficacy will vary depending on the density of receptors and downstream signaling molecules. In cases where receptors and/or signaling molecules are limiting, agonists with low intrinsic efficacy will act as partial agonists. However, if receptors and signaling molecules are sufficiently abundant, then two agonists of differing intrinsic efficacy will both operationally signal as full agonists. Thus, intrinsic efficacy is a property of the ligand and of the particular signaling pathway being examined, while partial agonism is operationally defined, is a function of receptor and downstream signaling molecules, and will vary from cell-to-cell depending on these factors. This is particularly important when comparing CB₂ agonist signaling in transfected cells versus their signaling in cells constitutively expressing CB₂ receptors, since in the latter CB₂ receptors are expressed at considerably lower levels. Thus, CB₂ agonists that have similar efficacy in transfected cells systems may behave as partial agonists in physiologically relevant systems.

The importance of inverse agonism is well appreciated in cannabinoid receptor signaling as most commonly encountered CB₁ receptor antagonists are inverse agonists (Fong and Heymsfield, 2009). Inverse agonists are best conceptualized by considering GPCRs as existing in multiple conformations, those that efficaciously activate G proteins and those that do not (Strange, 2002). Expressed in a cell, in the absence of ligand, most receptors will assume inactive conformations, but a few will adopt an active conformation. Those that are in an active conformation are referred to as being constitutively active. Note that multiple active conformations may exist, with some more strongly activating G proteins. Agonist binding will increase the number of receptors adopting active conformations, enhancing signaling, while inverse agonists will favor inactive conformations. Thus, inverse agonists will decrease basal signaling by the receptor. If this basal signaling is physiologically important, then inverse agonists can have profound effects. This has been proposed to be the situation for rimonabant and used as an explanation for some of rimonabant's actions (Fong and Heymsfield, 2009). Three features of inverse agonists/antagonists are of note. The first is that true neutral antagonists are quite rare. To be a neutral antagonist a compound needs to bind to the receptor without perturbing the equilibrium between active and inactive conformations, while nonetheless preventing the binding of other ligands. This probably explains why most neutral antagonists are relatively low affinity, though exceptions exist. The second is that in practice for cannabinoid receptors it is often quite difficult to distinguish between constitutive activity and activation by endocannabinoids. This is because that many of the approaches used to study CB₁ or CB₂ receptor signaling also stimulate the formation of endogenous cannabinoids. (For example, the preparation of membrane fractions.) Thus, careful experimentation is needed to establish whether "basal" signaling by CB₁ and CB₂ receptors is due to constitutive activity of the receptor or is due to

ongoing production of endocannabinoids. The third feature is that constitutive activity is proportional to receptor expression, thus inverse agonism is usually detected only under high levels of receptor expression. While these high levels of receptor expression are readily attained in transfected cell systems, they are more seldom reached in physiological systems, and the occurrence of constitutive activity and the relevance of inverse agonism in physiological systems is a matter of considerable debate.

Protean agonism combines low intrinsic efficacy with variable basal signaling of a receptor. Protean ligands are those that show low agonist efficacy. If basal signaling is low, then these compounds will act as an agonist, albeit often a partial agonist, stimulating signaling above the low basal levels. Conversely, if basal signaling is high, then protean agonists will decrease the level of signaling towards the maximal level that the ligand is capable of stimulating. AM1241 is an example of a CB₂ agonist that shows strong protean agonism in expression systems (Mancini et al. , 2009, Yao et al. , 2006).

2.4 Functional selectivity as it applies to CB₂ ligands

2.4.1 Functional selectivity of CB₂ agonists—The above discussion has treated GPCR signaling as a monolithic entity. However, the reality is more complicated. Robust evidence accumulating over the past twenty years clearly indicates that different GPCR agonists can differentially activate signaling pathways. Thus one agonist may be particularly efficacious in activating MAP kinase signaling while another will be more efficacious as an inhibitor of adenylyl cyclase. This concept can be easily rationalized by accepting that different ligands will favor different conformations of a GPCR, and these different GPCR conformations will interact more favorably, or not, with specific G proteins, leading to preferential activation of individual signaling pathways by distinct agonists. This process is referred to by several terms, including functional selectivity, agonist-induced trafficking, and biased agonism (Mailman, 2007, Urban et al. , 2007). We will refer to it as functional selectivity.

Functional selectivity has been found in CB₂ receptor signaling. One study examined the inhibition of adenylyl cyclase, release of intracellular calcium, and activation of MAP kinase, and found clear differences in rank order potency of different CB₂ ligands in the process—a hallmark of functional selectivity (Shoemaker, Ruckle, 2005). We recently systematically examined CB₂ functional selectivity and found striking differences in signaling among the commonly used classes of CB₂ agonists (Atwood et al. , In press). This study examined agonist-induced CB₂ receptor activation, beta-arrestin2 membrane recruitment, MAP kinase activation, and inhibition of voltage-dependent calcium channels. The most striking finding was that aminoalkylindoles (e.g., WIN55,212-2) failed to inhibit calcium channels or cause CB₂ receptor internalization, despite activating MAP kinase and recruiting beta-arrestin2 to the membrane. This is surprising as WIN55,212-2 and related aminoalkylindoles, such as AM1241 are widely and commonly used as CB₂ receptor agonists. However, these results show that aminoalkylindoles only activate a subset of the canonical CB₂ signaling pathways.

These findings of functional selectivity have major implications for the interpretation of some existing results and for the development of CB₂ receptor ligands. The first is that the label of “CB₂ agonist” is too simplistic. When speaking of a CB₂ agonist it is also necessary to specify the signaling pathway involved. The second is that we have little understanding of the relevant signaling pathways for the desired, or undesired, therapeutic actions of CB₂ agonists. For example, does CB₂ -mediated analgesia require calcium channel inhibition? The third is that by occupying the CB₂ receptor without productively signaling, a functionally selective agonist may prevent signaling by an endogenous ligand at the neglected pathway (i.e. serving simultaneously as agonist and antagonist depending on the

pathway polled). This greatly complicates the interpretation of experimental results. It may also explain some other puzzling results, such as the reported pro-inflammatory effects of CB₂ agonists in some model systems (Oka et al. , 2005). However it may also offer new opportunities for the development of fine-tuned, pathway specific therapeutics.

2.4.2 Functional selectivity of CB₂ receptor antagonists—While functional selectivity of GPCR inverse agonists has not been as intensively investigated as functional selectivity of GPCR agonists, conceptually it is identical to functional selectivity of GPCR agonists. Here, different inverse agonists will favor distinct inactive conformations of the GPCR, preferentially favoring uncoupling from one class of G proteins, while maintaining coupling to another. Thus, one inverse agonist may decrease the coupling of the receptor to MAP kinase while maintaining it to adenylyl cyclase, while another inverse agonist will have the opposite effect. In the study mentioned above, we found evidence for functional selectivity of SR144258 and AM630, where SR144258 acted as an inverse agonist for receptor internalization (increasing expression of cell surface CB₂) while AM630 acted as a neutral antagonist. However, in all other assays the two inverse agonists behaved similarly.

2.5 Concluding remarks

The full potential of CB₂ agonists as therapeutic agents remains to be realized. Based on what we know from the biology of CB₂ receptors and from preclinical studies, CB₂ receptors offer promise as therapeutic targets. However, data in the public domain from clinical trials of CB₂ agonists have been disappointing: Trials of CB₂ agonists from Pharmos, GSK, and Shionigi have either failed to meet their primary endpoints, or the compounds have been withdrawn from further clinical development. Possible reasons for this include inadequacies of preclinical models to predict clinical efficacy in humans, differences between the signaling of human and rodent CB₂ receptors, and insufficient consideration of the nuances of CB₂ pharmacology. The road forward to bring CB₂ agonists to the clinic will require a more careful matching between preclinical models and specific clinical trial indications, developing and using transgenic mice expressing human CB₂ in preclinical models, and establishing the pharmacological properties of CB₂—particularly which signaling pathways—that are most relevant to specific clinical indications. We feel that the development and characterization of new pharmacological tools will finally turn the potential of CB₂-based therapeutics into a reality.

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Abbreviations

CHO	Chinese hamster ovary
CNS	central nervous system
ERK	extracellular-regulated kinase
GPCR	G protein-coupled receptor
GRK	G protein receptor kinase
HEK	human embryonic kidney
JNK	c-jun N terminal kinase
MAP kinase	mitogen-activated protein kinase

PI3K	phosphatidyl inositol 3 kinase
PPAR	peroxisome proliferator-activated receptor
THC	Δ^9 tetrahydrocannabinol
TRP	transient receptor potential

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