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Overcoming the psychiatric side effects of the cannabinoid CB1 receptor antagonists: current approaches for therapeutics development

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Abstract

The cannabinoid receptor 1 (CBR1) is involved in a variety of physiological pathways and has long been considered a golden target for therapeutic manipulation. A large body of evidence in both animal and human studies suggests that CB1R antagonism is highly effective for the treatment of obesity, metabolic disorders and drug addiction. However, the first-in-class CB1R antagonist/inverse agonist, rimonabant, though demonstrating effectiveness for obesity treatment and smoking cessation, displays serious psychiatric side effects, including anxiety, depression and even suicidal ideation, resulting in its eventual withdrawal from the European market. Several strategies are currently being pursued to circumvent the mechanisms leading to these side effects by developing neutral antagonists, peripherally restricted ligands, and allosteric modulators. In this review, we describe the progress in the development of therapeutics targeting the cannabinoid receptor 1 in the last two decades.

Keywords

CB1 receptor; psychiatric side effects; neutral antagonists; peripherally restricted antagonists; allosteric modulators; therapeutics development

1. INTRODUCTION

The medicinal and psychoactive properties of marijuana have been known for centuries. The last few decades witnessed the discovery and cloning of two class A Rhodopsin-like G protein-coupled receptors, named cannabinoid 1 and 2 receptors (CB1R and CB2R), that mediate the biological effects of the main psychoactive constituent of *Cannabis sativa*, (−)-delta 9-tetrahydrocannabinol (Δ^9-THC). While found ubiquitously throughout the whole body, CB1R is preferentially localized at central and peripheral nerve terminals, mediating inhibition of neurotransmitter release [1]. CB2R is located primarily on blood and immune cells, modulating inflammatory responses [2]. These two receptors, together with their endogenous ligands and functional proteins involved in their synthesis, transport, and activation, make up the endocannabinoid system. The most well-known endogenous ligands,

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CONFLICT OF INTEREST

The authors confirm that this article has no conflict of interest.

also named endocannabinoids, are anandamide and 2-arachidonoylglycerol (2-AG). These endocannabinoids are synthesized on-demand from cell membrane arachidonic acid derivatives. They exert their effects for a short period before being removed from their site of action by degradation by fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL) [3].

Being one of the most abundant G protein-coupled receptors (GPCRs) found in mammalian brain, CB1R has received considerable attention for its role in many physiological processes including pain regulation, learning and memory, appetite and food intake, lipogenesis, and cravings [4–6]. A plethora of selective and non-selective CB1R agonists and antagonists have been developed, some of which are widely used as research tools such as the agonists CP55,940, WIN55,212–2, and AM251 [7–9]. However, no synthetic cannabinoids are currently in the clinics. The only FDA-approved dosage formulations of phytocannabinoids contain cannabidiol (CBD) and Δ^9-THC (or its synthetic analogue nabilone), and are used in clinics for the treatment of seizures, pain relief, appetite stimulation, and suppression of nausea and vomiting.

The observation that endocannabinoid are overactive in obese humans [10–12] and obese animals in both genetic and diet-induced obesity [13–14] has spurred research effort to develop CB1R antagonists for obesity treatment. After initial disappointing results with modifications of the structures of Δ^9-THC and the non-steroidal anti-inflammatory drug pravadoline, the first therapeutic agent to emerge from decades of cannabinoid research is the CB1R antagonist/inverse agonist rimonabant (SR141716, Acomplia®, Sanofi-Aventis). In 2006, rimonabant was licensed in United Kingdom for the treatment of obesity and related metabolic risk factors in nondiabetic and diabetic overweight and obese patients [15–18]. Rimonabant showed improvement in glycemic control and lipid profile in type 2 diabetic patients [19], as well as loss of visceral and hepatic fat in abdominally obese patients [20]. It also demonstrated positive effects for smoking cessation [21–22]. Unfortunately, it was subsequently withdrawn from the European market in 2008 due to occurrence of psychiatric adverse effects such as depression, anxiety, and even suicidal ideation. Other concerns noted with CB1R antagonists/inverse agonists included increased incidence of headache, irritability, insomnia, dizziness, nausea, vomiting, malaise and pruritus [23]. Prompted by the risk of these untoward side effects, the pharmaceutical industry terminated ongoing clinical trials of other brain-penetrant CB1R antagonists such as the longer acting second generation surinabant (SR147778, Sanofi-Aventis), ibipinabant (SLV319, Solvay Pharmaceutical), taranabant (MK-0364, Merck), and otenabant (CP-945,598, Pfizer) (Fig. 1).

Given the current lack of effective treatment for obesity and drug addiction, and the important physiologic role CB1R plays as one of the most abundant GPCRs in the CNS, novel strategies have been explored to eliminate or mitigate the central psychiatric adverse effects of the CB1R signaling pathway but retain the pivotal therapeutic benefits of CB1R inhibitory mechanism. These strategies include the development of CB1 receptor neutral antagonists, peripherally restricted antagonists, and allosteric modulators.

1. **Neutral antagonists**: The CB1R is known to possess constitutive activity that is crucial for a variety of cellular processes to maintain homeostasis [24]. As a result, inverse agonism at the CB1R reducing or blocking this constitutive activity could lead to long-lasting effects on CB1R function that might have clinical ramifications [25]. Neutral antagonists that antagonize endocannabinoids but do not change the basal CB1R activity are expected to be devoid of the potential downside consequences of inverse agonism at CB1R, thus having therapeutic potential in pathological conditions due to excessive receptor activation [26].

2. **Peripherally restricted antagonists**: There is increasing evidence in both animal and human studies supporting the premise that the effects of CB1R antagonists in weight loss and metabolic diseases can be produced at peripheral sites and through cell-signaling mechanisms without requiring involvement of the CNS-receptor mediated actions [15,17,27–28]. Therefore, peripherally restricted CB1 receptor antagonists that have no blood-brain barrier (BBB) penetration and limited CNS exposure are expected to retain certain therapeutic efficacy in the treatment of obesity and diabetes without the liability of CNS side effects.

3. **Allosteric modulators**: GPCR allosteric modulators modulate the activities of orthosteric agonists by binding to the allosteric binding site(s) which is/are topologically distinct from and often less highly conserved than the orthosteric binding site. They exert biological effects only in the presence of orthosteric ligands. Therefore, GPCR allosteric modulators may offer greater subtype selectivity, selective spatial and temporal signaling, and effect “ceiling” (thus lower risk of over dosing). Importantly, the CB1R allosteric modulators disclosed so far appear to have reduced inverse agonism [29–30]. Further, since the endocannabinoids are transiently released on demand and removed from their sites of action by cellular uptake, CB1 allosteric modulators may not have a long-lasting effect compared to orthosteric ligands. These signaling properties suggest that allosteric modulators may have inherent advantages in therapeutic applications involving CB1R.

In this review, we will summarize the ongoing efforts in these three approaches to target CB1R signaling pathways in a more selective and specific manner to minimize the psychiatric side effects. Each class of compounds will be discussed in the chronological order of their disclosure.

2. NEUTRAL ANTAGONISTS

It has been established that the endocannabinoid system exists in a tonically active state in most tissues examined [31–32]. At a basal state, a constitutively active receptor exists in an equilibrium between active state and inactive state and probably some intermediate states [33]. Upon binding, an agonist shifts the equilibrium favoring the active state, triggering downstream physiological effects, whereas an inverse agonist shifts the equilibrium from the basal state to the inactive state. Thus CB1R basal functional activity could play an important

role in maintaining cellular homeostasis [24]. As a result, reduction of basal levels of the CB1R active state, in the absence of decreased neurotransmitter release, could lead to pharmacological ramifications including untoward side effects. As endocannabinoids are found to be elevated in pathological conditions, a neutral antagonist which blocks signaling tone, but does not reduce the basal level of active state receptor, could be a safer therapeutic option than those produced through receptor blockade and inactivation [26].

Though withdrawn from the market, SR141716 still remains a valuable research tool and extensively used as the prototypic selective CB1R inverse agonists. The pyrazole scaffold of SR141716 has been widely used as the starting point for side chain modifications in newer generations of CB1R antagonists as depicted in Fig. 2. Other non-pyrazole-based neutral antagonists are shown in Fig. 3.

2.1 Pyrazole derivatives

VCHSR—VCHSR is one of the first reported neutral antagonists. It was designed from molecular modeling studies which demonstrated the critical role of the residue Lys192$^{3.28}$ in the inverse agonism of SR141716 by preferential binding to the carboxamide group in the inactive CB1R state [34–35]. The carbonyl oxygen was therefore removed by modification of the amide to an ethenyl moiety to eliminate hydrogen bonding capability at the C3 position but preserve the carboxamide *trans* geometry.

VCHSR attenuated WIN55,212-induced hCB1R-mediated inhibition of calcium current in rat superior cervical ganglion neurons but had no effect when administered alone up to 10 μM [34]. When administered on the first postnatal day in mice, VCHSR inhibited milk ingestion and growth, similar to SR141716 albeit the effects were milder [36].

PIMSR—PIMSR is another pyrazole derivative which was designed computationally to stabilize both the active and inactive states of CB1R to afford neutral antagonism [37]. The C3-carboxamide moiety of the pyrazole scaffold was substituted by an imine group in PIMSR to remove interaction with the Lys192$^{3.28}$ residue. Similar to VCHSR, PIMSR had no effect in the calcium flux functional assay alone, unlike SR141716 which exhibited an increase in calcium flux [37].

The CNS-penetrant PIMSR was shown to be devoid of dysphoric effects in electrical brain stimulation reward studies [38]. This encouraging result prompted the studies of its metabolic effects in rodents. PIMSR was found to reduce weight, food intake, adiposity, and alcohol-induced hepatic steatosis following an acute administration of a high level of ethanol. In addition, PIMSR improved glycemic control and lipid homeostasis in obese mice caused by a high-fat diet. Though PIMSR partially prevented alcohol-induced alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactic acid dehydrogenase (LDH) in the binge alcoholic hepatic steatosis model, it was found to elevate ALT and liver weight which are markers of liver injury with chronic administration in the obese mice model. The elevation of ALT level by PIMSR treatment was proposed to be unlikely due to the CB1R neutral antagonism as other neutral antagonists, such as AM6545, did not induce liver injury [38].

AM4113—First reported in 2007 [39], AM4113 is one of the most extensively characterized CB1R neutral antagonists and widely used as a pharmacological tool to study the CB1R signaling pathways. AM4113 is an analogue of SR141716 without the piperidinyl group ring at the C3-carboxamide. In competitive [^{3}H]CP55,940 binding assays, AM4113 had a K_i value of 0.80 ± 0.44 nM and exhibited a 100-fold selectivity for CB1R over CB2R [40]. AM4113 had no effect on the forskolin-stimulated cAMP accumulation in CB1R-transfected HEK-293 cells up to 10 μM concentration [40].

As expected with CB1 receptor antagonism, AM4113 attenuated the effects of the agonist AM411 in the cannabinoid tetrad test (locomotion, analgesia, catalepsy, and hypothermia) [24,39], and blocked hypothermia induced by CP55,940 [40]. AM4113 also reduced food intake and weight gain in rats [39–40], which was confirmed to be CB1R-mediated using CB1R knockout rats [41]. Finally, AM4113 demonstrated no effect on conditioned gaping or vomiting in rats [40] and ferrets [42].

AM4113 also displayed positive profiles as a promising potential for the treatment for abuse of opioids, nicotine, marijuana, and binge alcohol drinking in numerous behavioral studies. Like AM251, pretreatment of AM4113 attenuated the aversive affective properties of naloxone-precipitated morphine withdrawal in rats [43]. AM4113 significantly attenuated nicotine taking behavior, motivation for nicotine, cue-, priming- and stress-induced reinstatement of nicotine-seeking behavior in rats. In mice, AM4113 suppressed ethanol consumption and preference without any significant effects on body weight, ambulatory activities, and preference for taste such as saccharin and quinine [44]. AM4113 could substitute for rimonabant in the rimonabant-induced conditioned suppression of saccharin drinking [45]. In nonhuman primate studies, both AM4113 and SR141716 surmountably antagonized the discriminative stimulus effects of the CB1R full agonist AM4054 [46]. In squirrel monkeys, both AM4113 and SR141716 attenuated nicotine- and THC-seeking behaviors in both active addiction and relapse models, as well as cue-induced reinstatement of self-administration of cocaine [47].

Importantly, AM4113 is devoid of many untoward effects associated with CB1R inverse agonists. Pretreatment with AM4113 had no effect on food intake or anxiety, yet demonstrated antidepressant-like effects [48]. Unlike another antagonist/inverse agonist AM251, AM4113 did not enhance retention of contextual fear conditioning in rats [49]. The whole gut transit time in mice was not reduced by AM4113, in contrast to the shortened transit time seen with CB1R inverse agonists [50]. AM4113 attenuated some of the depressive effects of WIN55,212–2 in behavioral profiles in open-field studies, including ambulation, rearing, circling, and the increased latency to leave the middle start area of the open-field arena [42]. However, like SR141716, AM4113 dose-dependently increased the level of scratching and grooming [42], altered the natural satiation in rats such as excessive grooming [51], and precipitated cannabinoid withdrawal signs [52].

Pharmacokinetic studies indicated that AM4113 had poor bioavailability, but was able to penetrate the BBB, and was subsequently eliminated more slowly from brain than plasma [44]. Though useful as a research tool, the lack of oral bioavailability limits its development as a clinical candidate [53].

AM6527—Replacement of the 4-chlorophenyl substituent by the 4-iodophenyl group at the C5 of the pyrazole template led to AM6527 which is an orally active CB1R neutral antagonist. AM6527 has lower binding affinity to rat CB1R and maintained the same 100-fold selectivity in relative to the hCB2R like AM4113. In the food-reinforced behavior experiments in rats, both AM6257 and AM4113 had similar ED_{50} values when administered intraperitoneally; however, only AM6527 was effective following oral administration (ED_{50} = 1.49 mg/kg), whereas AM4113 showed no effects up to oral doses of 32 mg/kg [53].

Like AM4113, AM6527 pretreatment prevented naloxone-precipitated morphine withdrawal in the conditioned place aversion (CPA) paradigm. However, orally administered AM6527 was also observed to suppress locomotor activity during conditioning [43].

NESS06SM—NESS06SM is a condensed tricyclic pyrazole derivative of SR14716 [54]. It exhibited nanomolar affinity to CB1R (K_i = 10.25 nM) and good selectivity relative to CB2R (K_i CB2R > 5000 nM). It behaved as a neutral antagonist in the [^{35}S]GTPγS assay [54]. In silico parameters suggested that NESS06SM exhibited sparing BBB permeability. Chronic treatment with NESS06SM reduced body weight and cardiovascular risk factors in diet induced obesity mice fed with fat diet. More importantly, chronic administration of NESS06SM did not alter mRNA expression of both monoaminergic transporters and neurotrophins associated with anxiety and mood disorders [54]. Furthermore, cotreatment with NESS06SM reduced food intake and weight increment, attenuated common side effects caused by chronic administration of the atypical antipsychotic, olanzapine and restored all blood parameters without altering the positive behavioral effects of olanzapine [55].

ABD459—ABD459 exhibited a binding affinity K_i of 8.6 nM for murine CB1R. It antagonized CP55,940-induced [^{35}S]GTPγS binding without affecting the basal receptor constitutive activity, thus demonstrating properties as a CB1R neutral antagonist. Intraperitoneal administration of ABD459 (3–20 mg/kg) inhibited food consumption in nonfasted mice with no rebound after washout. It did not alter motor activity. ABD459 decreased rapid eye movement (REM) sleep with no effects on wakefulness and non-REM sleep [56].

Other Pyrazole derivatives—Using bioisoteric replacement of the C3-carboxamide of the SR141716 with vinyl fluoride, the Lazzari lab reported the pyrazole derivatives (±)-**12** and (*Z*)-**13** [57]. These two compounds exhibited lower binding affinities and selectivity for CB1R than SR141716. Pharmacological characterization in the [^{35}S]GTPγS binding and mouse vas deferens assays supported their neutral antagonist profiles. (Z)-**13** at 20 mg/kg (i.p.) produced the same reduction in food intake as 10 mg/kg of SR141716 yet no observable adverse effects were evidenced for (Z)-**13** at 20 mg/kg [57].

2.2 Non-pyrazole-based CB1R neutral antagonists

Thioamide—Boström et al from AstraZeneca performed scaffold hopping to replace the pyrazole core of SR141716 with a pyrazine and modified the carboxamide to thioamide [58]. Pyrazine-2-thioamide **14** was confirmed to be a neutral antagonist in the [^{35}S]GTPγS binding assay with the same potency as SR141716 (**14**, IC_{50} = 2.4 nM). Compound **14** was

found to be able to cross the BBB; however, its solubility remains poor (< 0.1 μM). Oral administration of **14** reduced body weight in cafeteria diet induced obese mice which remained after a 1–2 week washout period, a phenomenon not seen with SR141716 [58].

Tetrahydrocannabivarin (THCV)—Δ^9-Tetrahydrocannabivarin (THCV), naturally found in *Cannabis*, is a homologue of Δ^9-THC with a propyl side chain instead of a pentyl group (Fig. 3). [^{35}S]GTPγS binding studies indicated that THCV acted as a CB1R neutral antagonist at low doses [32]. However, at higher doses, it can behave as a CB1 agonist like Δ^9-THC. THCV could act either as CB2R agonist or antagonist depending on the assays [59–62].

THCV produced hypophagic effects in both fasted and non-fasted mice [63]. While it did not significantly impact food intake or weight gain, THCV produced an early and transient increase in energy expenditure. THCV dose-dependently reduced glucose intolerance in genetically obese mice and improved glucose tolerance and enhanced insulin sensitivity in diet-induced obese mice [64].

In human trials, THCV treatment increased neural responding to rewarding and aversive stimuli [65]. Using magnetic resonance imaging, another study in humans revealed that THCV decreased resting state functional connectivity in the default mode network and increased connectivity in the cognitive control and dorsal visual stream networks, brain regions where functional connectivity are found to be altered in obesity [66].

Cannabidiol-based derivatives O-2050 and O-2654—6”-Azidohex-2”-yne-cannabidiol (O-2654) was suggested to be a CB1R neutral antagonist as it could antagonize the inhibitory effect of WIN55,212–2 in the mouse vas deferens but did not amplify the electrically evoked contractions like SR141716A [67]. No other studies have been reported on this compound.

A sulfonamide analogue of Δ^8-THC with an acetylenic side chain, O-2050, was initially proposed as CB1R neutral antagonist as it produced potent antagonism of WIN55,212–2 and CP55,940 but showed no inverse agonist property in the myenteric plexus-longitudinal muscle (MPLM) preparation of guinea-pig small intestine [32]. However, subsequently, the neutral antagonist property of O-2050 was found to be assay-dependent. Even though O-2050 antagonized the cannabinoid effects in the [^{35}S]GTPγS binding and mouse vas deferens assays without exhibiting any activity alone in either assay, it inhibited forskolin-stimulated cAMP signaling and produced similar effect in a mouse drug discrimination procedure like THC [68]. O-2050 also facilitated noradrenaline release and potentiate the CB1R inverse agonistic effects of SR141716 in the guinea pig hippocampus [69]. These latter results suggest that O-2050 is not a viable CB1R neutral antagonist.

Amauromine—Diketopiperazine alkaloid amauromine from the fungus *Auxarthron reticulatum* is derived from the marine sponge *Ircinia variabilis*. It had a moderate binding affinity to hCB1R (K_i = 178 nM). cAMP assays suggested that it behaved as a CB1R neutral antagonist with K_b = 66.6 nM [70], although further studies are needed.

JWH-018-N-(5-hydroxypentyl) β-D-glucuronide (018-gluc)—018-Gluc is a glucuronide metabolite of JWH-018, a synthetic cannabinoid found in K2/Spice preparations produced through hydroxylation by cytochrome P450s and subsequent glucuronidation by UDP-glucuronosyltransferases. 018-Gluc was reported to be a CB1R neutral antagonist based on the characterization from the [^{35}S]GTPγS binding assay [71].

3. PERIPHERALLY RESTRICTED ANTAGONISTS

The main concerns about rimonabant that led to its withdrawal from the market were its CNS-mediated adverse effects. Growing evidence suggests that blockage of CB1R activity in peripheral tissues such as liver, muscle, adipocytes, and pancreas is adequate to suppress food intake, increase energy expenditure and reduce lipogenesis in both liver and adipose tissues [15,17,27–28]. Thus, a straightforward strategy to retain peripherally-mediated cannabinoid receptor therapeutic activity in metabolic disorders while eliminating adverse centrally-mediated effects is to develop peripherally restricted CB1R antagonists.

Common strategies to minimize CNS penetration in the development of peripherally restricted ligands include introduction of polar functional groups and addition of hydrogen bond donors. The topological polar surface area (TPSA), defined as the surface sum of all polar atoms such as oxygen and nitrogen, is a widely used parameter to predict the passive diffusion of a molecule through the BBB. Molecules with TPSA greater than 120 Å^2 typically have poor membrane permeability [72]. A TPSA value of less than 70 Å^2 tends to favor BBB permeability [72–73]. Thus, the most common strategy to design peripherally restricted ligands is to incorporate polar groups that increase TPSA values. A second strategy is to include permanently charged moieties that cannot pass through BBB passively and can only be transported across the BBB by special transporters. A third strategy is to introduce molecular features that enhance the propensity to become substrates of efflux proteins such as P-glycoproteins.

As the development of CB1R peripherally restricted antagonists up to 2013 has been reviewed in detail before [74], herein we will focus on the updates in this area since then. Similar to CB1R neutral antagonists, the pyrazole core of SR141716 also serves as the starting point for side chain modifications and scaffold hopping in the development of peripherally restricted CB1R antagonists. These compounds can act as either inverse agonists or neutral antagonists.

3.1. Pyrazole-based peripherally restricted CB1R antagonists.

AM6545—AM6545 is a peripherally restricted CB1R neutral antagonist. AM6545 has reasonable binding affinity to rat CB1R with K_i value of 1.7 nM, and exhibited a 302-fold or 38-fold selectivity in affinity relative to mouse CB2R and human CB2R, respectively [75]. As a neutral antagonist, AM6545 had no effect on the forskolin-stimulated cAMP level up to 3 μM, unlike the inverse agonist AM251 which stimulated cAMP production [75].

As one of the first reported peripherally restricted CB1 antagonists, AM6545 has been assessed in numerous behavioral models. AM6545 strongly suppressed the intake of high carbohydrate, high fat, and high sucrose diet with no or little impact on standard lab chow

diet [76–77]. AM6545 inhibited refeeding in fasted rats [78]. It inhibited food intake in CB1R gene-deficient mice, but not in CB1R/CB2R double knockout mice [75]. AM6545 did not affect food handling, instead, it reduced time spent feeding and feeding rate [76]. Unlike SR141716, AM6545 did not induce the initial transient decrease in food intake but a slight decrease was evident later during the treatment period [79]. However, AM6545 did not affect total caloric intake [79].

AM6545 demonstrated a marked reduction of body weight and fat mass in obese mice [79] [80]. Although AM6545 did not have an impact on lean mass, the metabolic profile of these obese mice was significantly improved [79]. Dyslipidemia (elevated serum triglyceride, total cholesterol, free fatty acids), glucose intolerance, and hyperinsulinemia, hormone dysregulation and hepatic steatosis were alleviated upon treatment with AM6545 [79–81]. Beneficial for diabetic nephropathy, AM6545 reduced diabetes-induced albuminuria and prevented nephrin loss both in vivo and in vitro in podocytes exposed to glycated albumin [82]. AM6545 exhibited synergistic effect with the CB2R agonist AM1241, displaying better efficacy in abolishing diabetes-induced renal monocyte infiltration and M1/M2 macrophage imbalance in vivo [82].

Pretreatment of AM6545 (i.p.) reversed the depressant effects of CP55,940 for all four cardiovascular parameters into stimulatory ones (diastolic blood pressure, systolic blood pressure, mean blood pressure, and heart rate) [83]. AM6545 (i.p.) markedly attenuated or delayed the lung inflammation and fibrosis in a murine model of radiation-induced pulmonary fibrosis and enhanced animal survival as in the genetic deletion studies [84]. AM6545 did not cause liver injury [38], and was able to reverse the slowing effect of WIN55,212–2 on colonic motility [75].

AM6545 is devoid of many centrally mediated untoward effects. In contrast to AM251, AM6545 had no/little nausea and vomiting side effects in animal studies. It did not produce gaping or conditioned taste avoidance in rats [75]. In addition, AM6545 did not potentiate LiCl-induced conditioned gaping nor reduced sucrose palatability [85]. Unlike AM4113, AM6545 did not precipitate cannabinoid withdrawal signs [52], or substitute for SR141716 in the rimonabant-induced conditioned suppression of saccharin drinking [45]. Also different from AM251, AM6545 did not affect the fixed consecutive number task, a test to measure choice to terminate a chain of responses prematurely following systemic blockade of WAY100,635, an $5HT_{1A}$ antagonist in rats [86].

Though AM6545 has a more limited brain penetration than AM4113, its brain-to-plasma ratio remains high at 0.20 to 0.41 for several hours after intraperitoneal administration, thus complicating the assessment of the contributions of CB1R-mediated peripheral and central mechanisms to its behavioral effects [75].

TM-38837—TM-38837 (structure not disclosed) was discovered internally at 7TM Pharma. In 2010, 7TM Pharma announced that it successfully completed a Phase I clinical trial for TM-38837 demonstrating that TM-38837 did not display the typical psychomimetic effects of THC at therapeutically relevant doses [87]. TM-38837 at 100 mg (p.o.) had no measurable feeling of high or body sway effects and limited heart rate effects [88].

TM-38837 was found to induce larger effects on inhibition of THC-induced heart rate increases than on THC-induced visual analogue scale of feeling high, consistent with its preference for peripheral target sites [89]. In PET studies in cynomolgus monkeys, expected clinical therapeutic doses of 20 mg demonstrated low levels of in vivo brain CB1R occupancy compared with SR141716 [90]. Unfortunately, 7TM Pharma has discontinued its business and there has been no further news on the development of TM-38837.

Pyrazole derivatives (Maitra lab)—In an effort to limit brain penetration, the Maitra lab modified the C3-carboxamide function of the pyrazole scaffold by incorporating permanently charged moieties such as alkyl pyridinium salts and N-oxides and groups with high TPSA values such as sulfonamides, sulfamides, piperidines functionalized with carbamates, amides, and sulfonamides [91–93]. Compound **21** (Fig. 4) was identified to have good CB1R antagonist potency, moderate selectivity over CB2R, and good metabolic stability. In vivo pharmacokinetic testing indicated that **21** has good oral bioavailability and minimal brain penetration [93].

Pyrazole derivative (Shia lab)—After several rounds of optimization at the C5 position of the pyrazole scaffold [94–95], the Shia lab presented compound **22** (Fig. 4) with excellent binding affinity (CB1R K_i = 0.3 nM), in vitro potency (EC_{50} = 3 nM), and limited CNS penetration (brain-to-plasma ratio 1:64). **22** had significant efficacy in reducing weight in a diet-induced obese mouse model and displayed a clean off-target binding screen against 163 other receptors [96].

TXX-552—TXX-552 is a peripherally restricted CB1R neutral antagonist disclosed recently with a brain:plasma ratio of 0.02 in rats [97]. It dose-dependently reversed WIN55,212–2-induced inhibition of forskolin-stimulated cAMP accumulation but did not increase the forskolin-induced cAMP level alone, indicating a lack of inverse agonist activity. It demonstrated good CB1 binding affinity and selectivity over the CB2R. In vivo studies confirmed that TXX-552 had minimal brain penetration and good oral bioavailability. TXX-552 decreased body weight of diet-induced obese mice, although the effect was less pronounced than observed with SR141716 at the same dose of 5 mg/kg. In contrast to SR141716, TXX-552 had no impact on acute food consumption by mice; however, TXX-552 was found to decrease fasting blood glucose and insulin levels, ameliorate glucose intolerance, reduce both serum triglyceride and total cholesterol levels. No adverse effects on physical appearance, behavior, or other signs of toxicity including lethargy, mania, or alteration of excreta were observed during the treatment with TXX-552 [97].

3.2 Non-pyrazole-based peripherally restricted CB1R antagonists

Triazole LH-21: A medicinal chemistry effort to investigate triazoles as the core structure in place of the pyrazole of SR141716 led to the identification of LH-21 as a CB1R neutral antagonist based on the mouse vas deferens and guinea pig ileum assays [98]. LH-21 has relatively low binding affinity to both human and rat CB1R (K_i values in the 630 – 855 nM range) [98–99]. While it initially appeared to have limited brain penetration and have silent antagonist activity [98], subsequent studies by Chen et al indicated that LH-21 was brain

penetrant (~1:1 brain-to-plasma ratio), and acted as an inverse agonist in the cAMP assay [99].

LH-21 had no effect on nociception, temperature, spontaneous motility, and catalepsy in cannabinoid tetrad test [98]. LH-21 did not affect feeding by acute administration in free feeding animals but was highly effective in blocking ghrelin-induced hyperphagia [100]. LH-21 was found to improve glucose handling in diet-induced obese pre-diabetic mice [101]. However, unlike SR141716, chronic administration of LH-21 (3 mg/kg) did not improve hypertriglyceridaemia, hypercholesterolaemia or liver fat deposits in Zucker rats [102]. LH-21 reduced feeding and body weight gain in both wild-type and CB1R knockout mice, suggesting that its appetite suppressant and anti-obesity effects are independent of action at the CB1R [99,102–104].

Anxiety-like behaviors and induction of complex motor activities such as grooming and scratching sequences were not observed with LH-21 [99]. Instead, it was observed to counteract obesity-induced anxiety, though this effect was proposed to be mediated by GPR55 receptor [101]. LH-21 only slightly reduced alcohol self-administration at a high dose of 10 mg/kg [104].

Pyrazoles JD5037 and JD5006—JD5037 and its analogue JD5006 are two peripherally restricted CB1 antagonists derived from the structure of ibipinabant (SLV-319) with a pyrazoline core instead of the pyrazole under a collaboration between Jenrin Discovery Inc. and National Institute of Health [105]. Both compounds showed good potency at the CB1 receptor (IC_{50} = 2 and 18 nM, respectively), lower BBB penetration as determined in the MDCK-mdr1 assay, and reduced brain receptor occupancy upon oral administration compared to SLV-319.

Preclinical studies in rodents and primates support the therapeutic benefits of JD5037 in suppressing progression of hepatic fibrosis. JD5037 was highly effective in inhibiting β–arrestin-2 activation, a marker in fibrotic disease progression [106]. When administered in the prediabetic stage, JD5037 prevented or reversed progression of type 2 diabetic nephropathy development in Zucker diabetic fatty rats [107]. JD5037 also attenuated the induction of tumor promoting genes in chemically-induced hepatocellular carcinoma [108].

JD5037 has demonstrated positive effects on metabolic parameters associated with Type 2 diabetes and obesity in a variety of murine models. JD5037 was as effective as the globally acting CB1R inverse agonist, SLV319, in reducing appetite, body weight, hepatic steatosis, and insulin resistance, and improving glucose tolerance in diet-induced obese mice [109–110]. These effects on appetite and weight reduction are mediated by decreasing leptin expression and secretion by adipocytes, increasing leptin clearance via the kidney [109], and restoring sensitivity to endogenous leptin which elicits hypophagia via the re-activation of melanocortin signaling in the arcuate nucleus [111] and/or decrease in ceramide levels [110]. Daily chronic treatment with JD5037 (3 mg/kg/day for 28 days) reduced body weight, reversed hyperphagia, and improved metabolic parameters in an extreme obesity Prader-Willi syndrome (PWS) mouse model [112]. JD5037 exhibited stronger affinity than SR141716 to a human CB1R isoform (CB1b) which is highly expressed in β-cells and

hepatocytes, but not in brain. It potentiated adenylyl cyclase activation, thus stimulating insulin secretion in β-cells [113].

In December 2017, Jenrin Discovery Inc. received approval to start the Investigational New Drug (IND) application for JD5037 as a drug candidate to treat nonalcoholic steatohepatitis (NASH).

Purine derivatives—Though otenabant (**5**), a CB1 antagonist developed by Pfizer, has physicochemical properties usually associated with peripherally restricted compound, it is CNS permeable. X-ray structure suggested that the atypical lower polarity of otenabant was attributed to the intramolecular H-bonding between the primary amide and the ethyl amine portion of the molecule [114]. Therefore, the Maitra lab sought to replace this portion of otenabant with other polar groups incapable of forming intramolecular H-bonding. This led to compound **31** with excellent potency on CB1R, 153-fold selectivity over CB2R, and good stability in human S9 microsomal fractions (>90% remaining after 120 min of incubation). In a rat PK assay, **31** demonstrated limited CNS penetration (brain to plasma ratios ranging from 0.05 to 0.11) [115]. Further optimization led to compound **33** which maintained good potency at CB1R, 50-fold selectivity over CB2R, low CNS penetration and good oral bioavailability. Oral administration of **33** did not reverse any centrally-mediated cannabimimetic effects of Δ^9-THC in the tetrad assay [116], consistent with its restriction to the periphery.

Switching the piperidine to piperazine for exploration of substitution on this piperazine ring led to compound **26** with good potency in calcium mobilization assay, excellent selectivity for CB1R relative to CB2R, good solubility in gastric pH, though limited solubility at pH 7.4. It has no detectable hERG activity in the [^{3}H]astemizole displacement assay. It demonstrated good half-life ($T_{1/2}$ = 90 min, CL=14 ml/min/kg) against human hepatic microsome preparations. After 10mg/kg oral administration, compound **26** was found predominantly in liver with some in plasma, and very little in brain. Compound **26** showed little to no blocking of temperature drop in rodent hypothermia model, confirming the low brain penetration. More importantly, p.o. administration of **26** was effective in reducing hepatic lipid accumulation in the murine alcohol-induced liver steatosis assay [117]. The urea analogue **33** was reported to have excellent CB1R antagonist potency, selectivity, oral bioavailability, and reduced brain penetration (Fig. 6) [118].

AM841—The hexahydrocannabinol AM841 is a peripherally-restricted covalent CB1R antagonist with relatively high CB1 affinity (K_i = 9 nM) [119]. Studies showed that AM841 reduced GI motility in normal and stressed mice, but demonstrated very little brain penetration and no characteristic centrally mediated CB1 receptor-mediated effects (analgesia, hypothermia or hypolocomotion) [120].

Tetrahydroindazole and Tetrahydropyrazolo[4,3-*c*]pyridine derivatives—Janssen Research & Development LLC reported two series of tetrahydroindazole (**28**) and tetrahydropyrazolo[4,3-*c*]pyridine (**29** – **30**) derivatives (Fig. 5) as peripherally selective CB1R inverse agonists (brain-to-plasma ratio < 0.1) [121–122]. These compounds exhibited

nanomolar potency against CB1R [121–122]. Oral administration of **28** once a day for 3 weeks resulted in lower plasma glucose levels in diet-induced mice [122].

4. ALLOSTERIC MODULATORS

The discovery that the CB1R contains allosteric binding site(s) has sparked an interest in pursuing CB1R allostery as an alternate approach to achieve therapeutic benefits while avoiding the inherent side effects of orthosteric ligands [123]. Allosteric modulators are generally categorized into positive allosteric modulators (PAMs) or negative allosteric modulators (NAMs), which positively or negatively modulate the affinity and/or efficacy of the orthosteric agonists, respectively [124]. A typical NAM reduces binding affinity of an orthosteric agonist, resulting in weakening signaling efficacy. In contrast, a subset of allosteric modulators demonstrates enhanced binding affinity of the orthosteric agonists but reduced functional efficacy of the orthosteric agonists. They are termed PAM-antagonists to distinguish its distinct operational model of allosterism compared to typical NAMs. Upon binding, these PAM-antagonists turn the receptor-G protein-orthosteric ligand-allosteric modulator complexes into inactive conformations, resulting in attenuation of efficacy of the orthosteric agonist through a “seek-and-destroy” mechanism. PAM-antagonists provide unique advantages in contrast to orthosteric antagonists and typical NAMs such as better reversal of ongoing persistent pathological overactivation and favorable target coverage in vivo [125].

Both PAMs and NAMs have been described recently in several reviews, including a detailed one from us [126], and herein we provide an update on CB1R NAMs with emphasis on those newly disclosed since 2017.

Indole-2-carboxamides

Organon reported the first CB1R allosteric modulators with an indole-2-carboxamide scaffold in 2005. Among these indole derivatives, the more widely investigated Org27569 displays a CB1R selective PAM-antagonist profile with positive binding cooperativity with the orthosteric agonist CP55,940, and reduction of efficacy of agonists in in vitro functional assays [123]. Org27569 demonstrates probe dependence with varying degrees of binding cooperativity with different orthosteric agonists. In a sharp contrast to strong positive binding cooperativity with CP55,490, Org27569 had close to neutral cooperativity with other orthosteric agonists such as HU-210, WIN55,212–2, Δ^9-THC, methanandamide, anandamide, and 2-AG [127–128]. Org27569 also displays a probe-dependent CB1R allosteric modulatory profile in a variety of in vitro functional assays, while it exhibits little or no inverse agonist activity alone [126].

Though only resulting in modest improvement of potency, structure-activity relationship (SAR) studies on Org27569 revealed the indole core and the 2-carboxamide function are critical. The ethylene linker and 4-dimethylamino or 4-diethylamino on the ring B are optimal. Shorter alkyl side chains at the C3 and electron-withdrawing substituents at C5 position of the indole ring are preferred [129–133].

The CNS-penetrant Org27569 reduced food intake in both CB1-deficient and wild-type mice [134]. It significantly attenuated the hypothermic effect of CP55,940 and anandamide [135] as well as both cue- and drug-induced reinstatement of cocaine- and methamphetamine seeking behavior like SR141716, supporting the potential benefits of Org27569 in treatment of drug addiction [126,135].

Diarylureas

Another CB1R modulator, PSNCBAM-1, reported by Prosidion Limited in 2007 shares a similar PAM-antagonist profile in vitro as Org27569 [30,126].

The first SAR studies revealed that alkyl substitution at the 2-aminopyridine moiety and electron-deficient aromatic groups such as cyano at the 4-chlorophenyl position are important for CB1 allosteric modulation [136]. The urea moiety was found to be critical for the modulatory activity [137]. Subsequently, it was found that the pyrrolidine ring is not required for the allosteric modulation [138], and the pyridine of PSNCBAM-1 could be replaced by other aromatic groups such as phenyl or five-membered heterocyclic rings [138–141]. Saturation binding studies on some of these compounds revealed that they increased [^{3}H]CP55,950 B_{max} but did not alter K_d values, implying their modulating CB1R by stabilizing low affinity receptors into a high affinity state [141].

Replacement of the 5-pyrrolidinylpyridine in PSCNABM-1 with 4-fluorophenyl resulted in RTICBM-74 (Fig. 8) with similar potencies as PSNCBAM-1 in calcium mobilization and [^{35}S]GTPγS binding assays but possessing significantly improved metabolic stability against rat liver microsomes (RTICBM-74: $T_{1/2}$ > 6 h, CL < 4.6 μL/min/mg vs. PSNCBAM-1 $T_{1/2}$= 13 min, CL = 114 μL/min/mg) [138]. Replacement of the 5-pyrrolidinylpyridine in PSCNABM-1 with 2-pyrrolyl group yielded RTICBM-229 (Fig. 8) with better potency in the [^{35}S]GTPγS binding assay (RTICBM-229 IC_{50} = 40 nM; PSNCBAM-1 IC_{50} = 115 nM), and greater cooperativity evidenced by significant increase of the maximal binding level of [^{3}H]CP55,490 (RTICBM-229 B_{max} = 5.87 pmol/mg, PSNCBAM-1 B_{max} = 4.53 pmol/mg) [141].

PSNCBAM-1 significantly reduced food consumption and body weight in an acute feeding rat model without any adverse effects on animal behavior and apparent signs of toxicity [30]. PSNCBAM-1 attenuated the reinstatement of extinguished cocaine-seeking behavior in rats [138]. Interestingly, the metabolically stable diarylurea RTICBM-74 is more effective than PSNCBAM-1 in this cocaine-seeking paradigm [138]. Unlike Org27569, PSNCBAM-1 caused a small but significant attenuation of Δ^9-THC-induced antinociception in mice [142]. Its structural analogue RTICBM-28 (Fig. 8) was able to reduce the potency of Δ^9-THC in drug discrimination assay, a phenomenon not seen with PSNCBAM-1 [142]. These differences in in vivo activities between these closely related analogues with similar in vitro potencies could be the result of variations in pharmacokinetics or binding kinetics to the CB1R target.

Pepcans

The α-hemoglobin-derived dodecapeptide (RVDPVNFKLLSH, pepcan-12) exhibited a typical allostery profile as expected for typical NAMs: decreasing both [^{3}H]CP55,940 and

[^{3}H]WIN55,212–2 binding levels and attenuating effects of agonists in a number of in vitro functional assays [143–144]. However, it also behaved as a partial agonist [143,145] and CB2R PAM in other assays [146].

Pregnenolone

Pregnenolone, an endogenous steroid hormone, was proposed to function as a CB1R NAM based on its ability to reduce Δ^9-THC-induced pERK1/2 activation in human CB1-CHO cells [147]. However, it had no effect on [^{3}H]CP55940 and [^{3}H]WIN55212–2 equilibrium binding, WIN55,212–2-inhibited pERK activation [127], or 2-AG signaling in autapic hippocampal neurons [144]. Animal studies showed that pregnenolone blocked the effects Δ^9-THC on locomotion, antinociception, hypothermia, catalepsy, food intake, memory impairment, glutamate and dopamine release [147], but had no impact on the effect of Δ^9-THC in drug discrimination paradigm [142].

Fenofibrate

Fenofibrate, a PPAR agonist, was reported as a CB1R NAM at high concentrations of 10–100 μM in radioligand binding assay, [^{35}S]GTPγS binding, total ERK expression and β-arrestin recruitment. At concentrations of less than 10 μM, it exhibited agonist activity in these assays [148].

Cannabidiol

Cannabidiol, a nonpsychotropic constituent of marijuana was reported to act as a CB1R NAM, reducing the efficacy and potency of 2-AG and Δ^9-THC on PLCβ, ERK, β-arrestin-2 recruitment, and CB1R internalization [149], as well as antagonizing the agonist activities of CP55,940 and WIN55,212–2 in the mouse vas deferens [150]. However, it demonstrated very weak binding affinity to CB1R (reported K_i values range from 4 to more than 10 μM) [150], and acted as a weak partial agonist in functional assays at concentrations more than 1 μM [149].

5. CONCLUSIONS AND FUTURE DIRECTIONS

The development of CB1R neutral antagonists, peripherally restricted antagonists and allosteric modulators has provided promising alternate approaches to the first generation globally acting orthosteric CB1 receptor antagonist/inverse agonist, rimonabant. These research efforts have significantly expanded our understanding of the CB1R receptor signaling pathways and pharmacology and demonstrated proof of concept for several alternative approaches to improve therapeutic utility and decrease adverse side effects. For example, reduction of food intake and weight gain and the production of other desired therapeutic actions can be achieved by selectively targeting peripheral CB1 receptor-mediated signaling processes or through allosteric of CB1 receptor conformation and function.

CB1 neutral antagonists provide the first “proof of concept” that “cleaner” compounds with little inverse agonism may achieve CB1R blockade as traditional antagonists/inverse agonist but have a more favorable pharmacological profile. For example, both CB1R inverse

agonists and neutral antagonists are able to reduce food intake and food-reinforced behaviors, but the latter do not cause nausea and vomiting [151]. In addition, neutral antagonists such as AM4113 appear to lack anxiogenic or depression-like effects associated with the inverse agonism at CB1 receptors in classical animal models such as elevated plus maze test. However, some of the side effects of CB1R inverse agonists still linger, such as AM4113 which produced anxiety-like effects similar to that seen with rimonabant in an open field assay [42]. Another complicating factor is the challenge to separate the pharmacological effects between pure antagonism and inverse agonism in a living system [152–153]. Finally, the long term anxiogenic or depressive effects of CB1R neutral antagonists have been investigated.

Similarly, peripherally restricted CB1R antagonists have been shown to retain many global antagonist effects, such as reducing feeding and weight gain and improving metabolic profile in coronary artery disease [154–155], liver and pancreatic disease [156], inflammatory disorders [156], and arthritis [157]. Importantly, many peripherally restricted CB1R antagonists do not show the centrally-mediated psychiatric side effects commonly observed with inverse agonists SR141716 and AM251. Among the two most advanced compounds in this class, TM-38857 was evaluated in a Phase I clinical trial before 7TM went out of business, whereas JD5037 was recently approved for IND application for the treatment of NASH. A positive clinical outcome of the front-running candidate JD5037 would validate this peripherally-restricted antagonist approach in targeting CB1R receptor for therapeutic benefits.

Allosteric modulation is a unique approach to target GPCRs such as the CB1R. Allosteric modulators offer many unique advantages over orthosteric ligands. They exert their effects only in the presence of endogenous ligands, allowing fine-tuning of their signaling instead of completely blocking the receptor function with exogenous cannabinoids. The probe- and pathway-dependence of allosteric modulators result in differential responses in different signaling pathways. Therefore, allosteric modulators can selectively target one specific endogenous agonist or a certain pathway for desirable therapeutic outcome. As previously discussed [126], allosteric modulators Org27569 and PSNCBAM-1 showed reduced inverse agonist effect, and therefore may have lower psychiatric side effects compared to SR141716 and other orthosteric antagonists/inverse agonists. Allosteric modulation can be useful for both central and peripheral therapeutic indications.

Mounting evidence supports CB1R antagonism as an important mechanism to manipulate the endocannabinoid signaling for the treatment of obesity, metabolic disorders, and drug dependence/substance abuse. Although the first generation CB1R antagonists have an unsatisfactory safety profile, newer classes of CB1R-targeted inhibitors such as neutral antagonists, peripherally restricted antagonists, and allosteric modulators offer promising alternate pharmacological approaches for the treatment of CB1R-mediated disorders. The exciting results discussed here represent the next step in a long journey, and much work is needed from both medicinal chemistry and pharmacology researchers to develop clinically useful CB1R-mediated therapeutic agents.

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LIST OF ABBREVIATIONS

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BBB	Blood-brain barrier
CB1R	Cannabinoid 1 Receptor
CB2R	Cannabinoid 2 Receptor
CBD	Cannabidiol
CL	Clearance
CNS	Central Nervous System
i.p.	intraperitoneal
p.o.	oral administration
LDH	Lactic Acid Dehydrogenase
MPLM	Myenteric Plexus-Longitudinal Muscle
NAM	Negative Allosteric Modulator
PAM	Positive Allosteric Modulator
SAR	Structure-Activity Relationship
Δ^9-THC	(−)-delta 9-Tetrahydrocannabinol
TPSA	Topological Polar Surface Area

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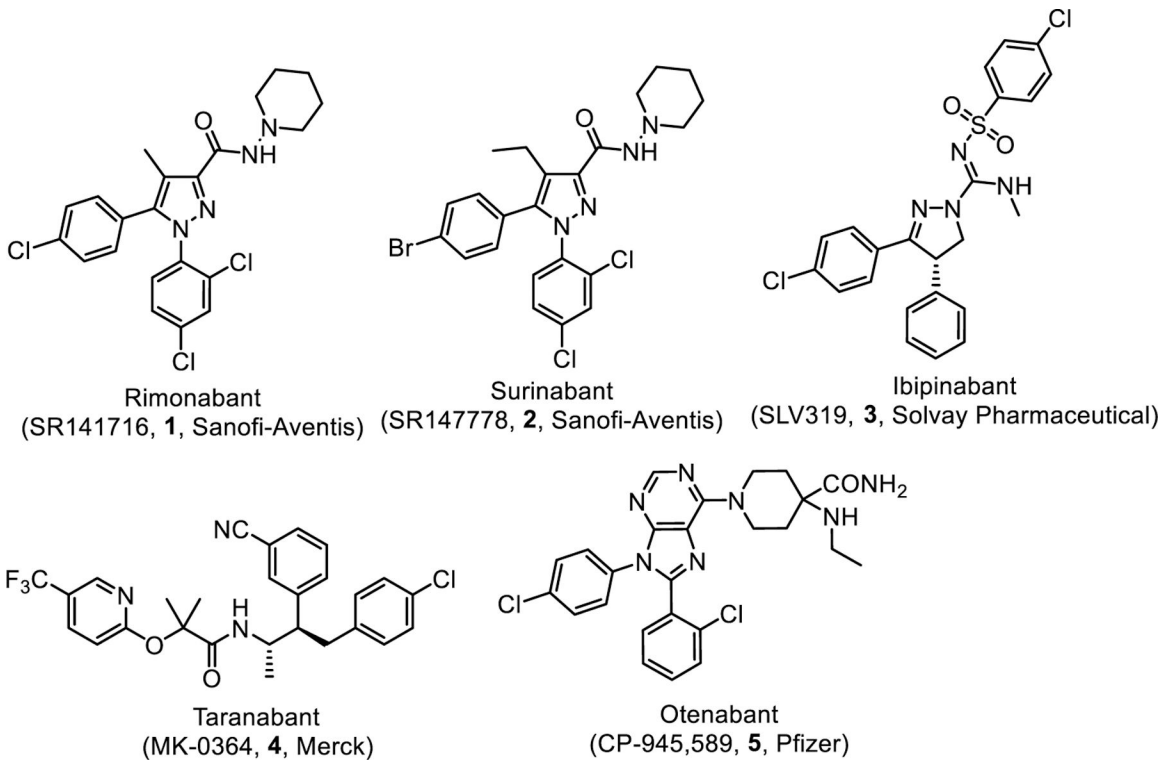


Fig. (1).
CB1R antagonists/inverse agonists that were advanced to clinical trials.

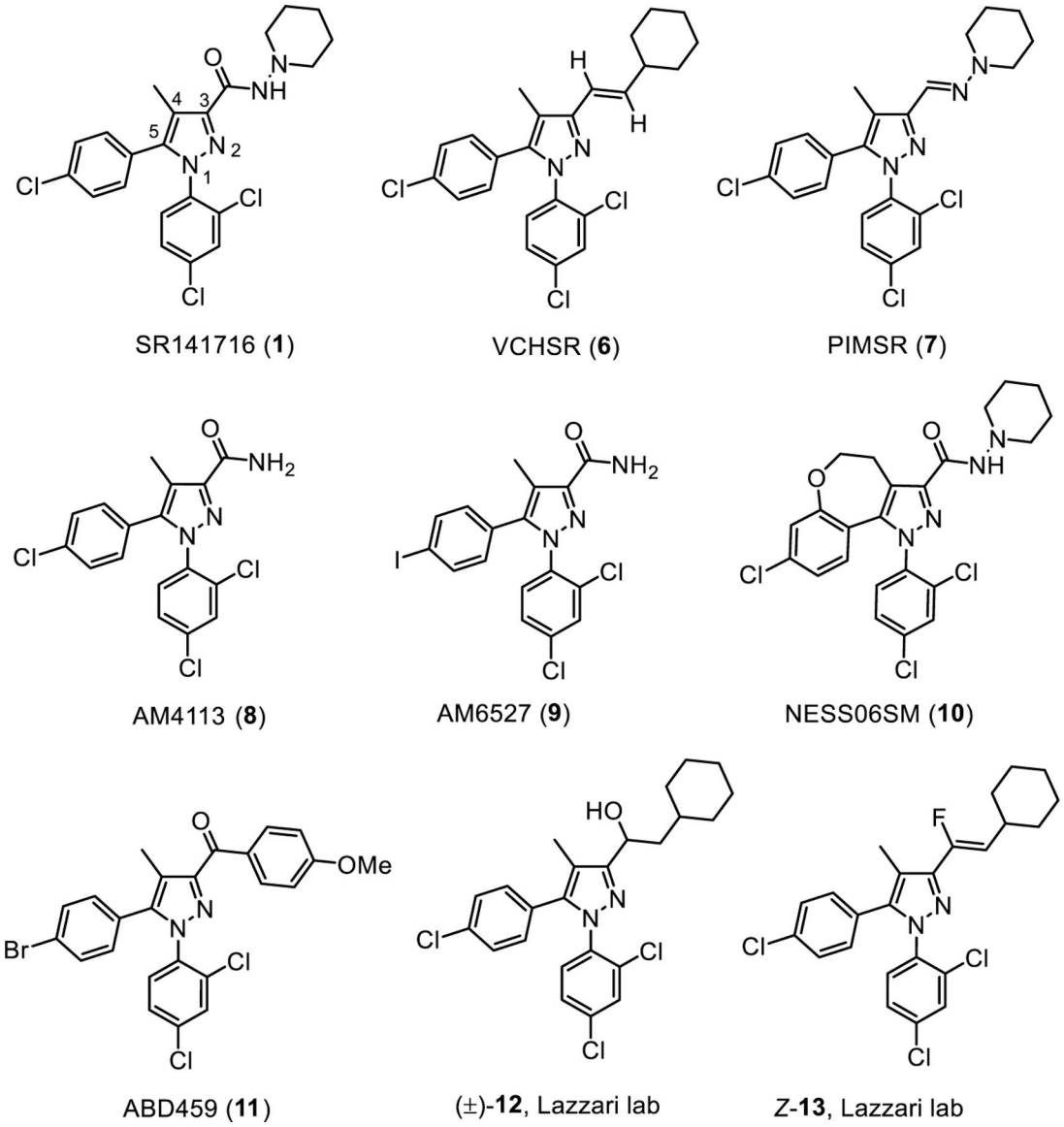


Fig. (2).
Structures of pyrazole-based CB1R neutral antagonists.

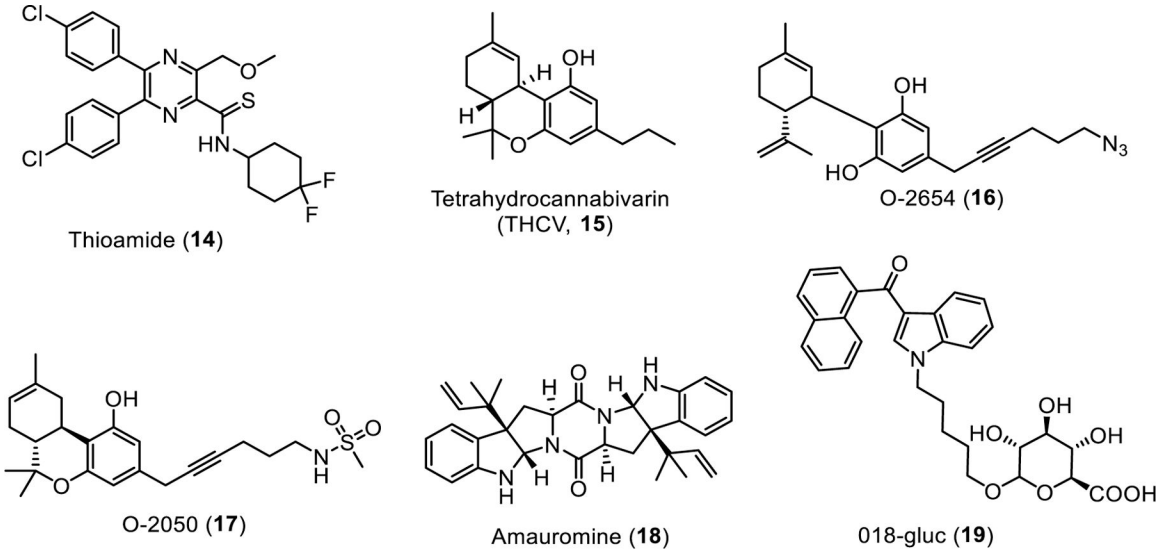


Fig. (3).
Structures of non-pyrazole-based CB1R neutral antagonists.

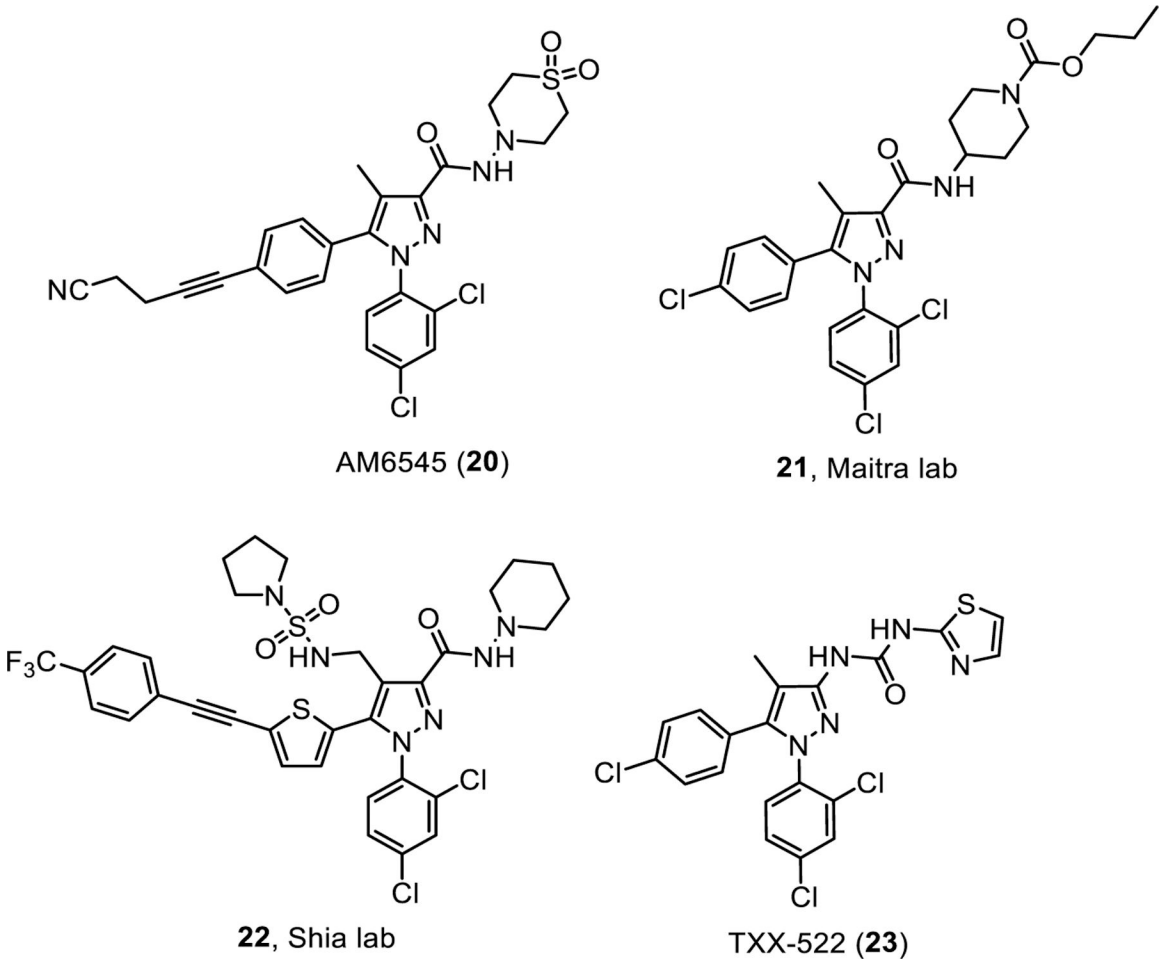


Fig. (4).
Structures of pyrazole-based peripherally restricted CB1R antagonists.

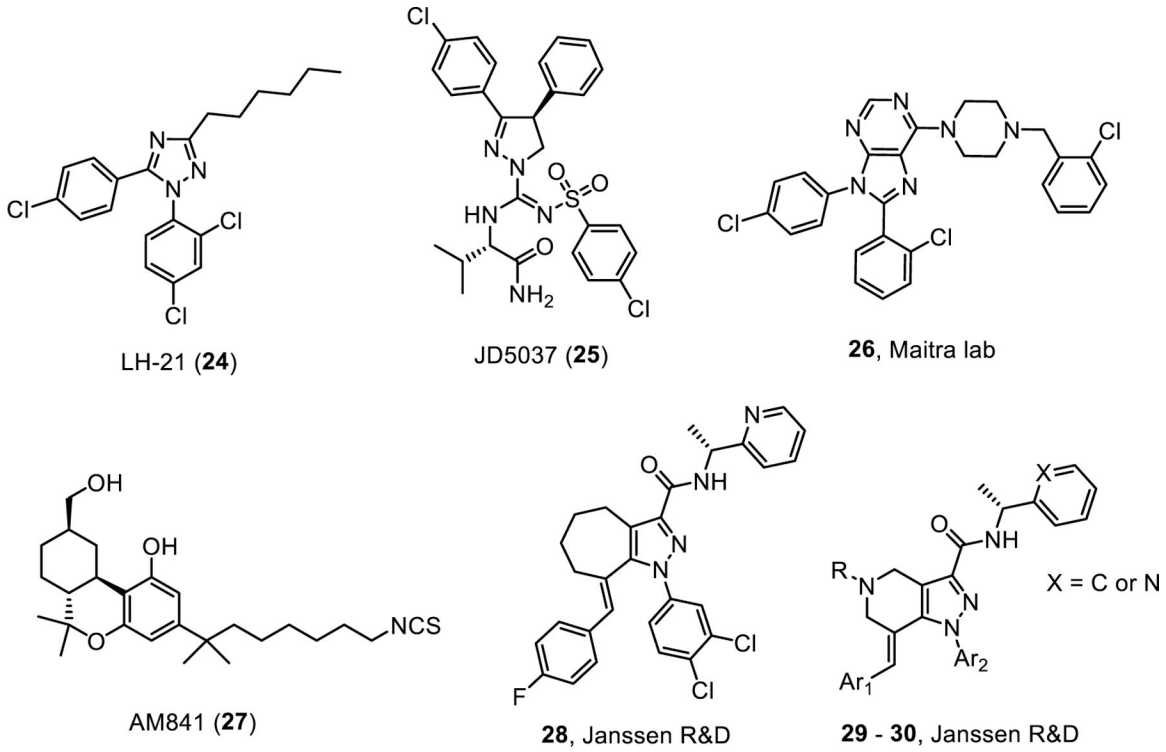


Fig. (5).
Structures of non-pyrazole-based peripherally restricted CB1R antagonists.

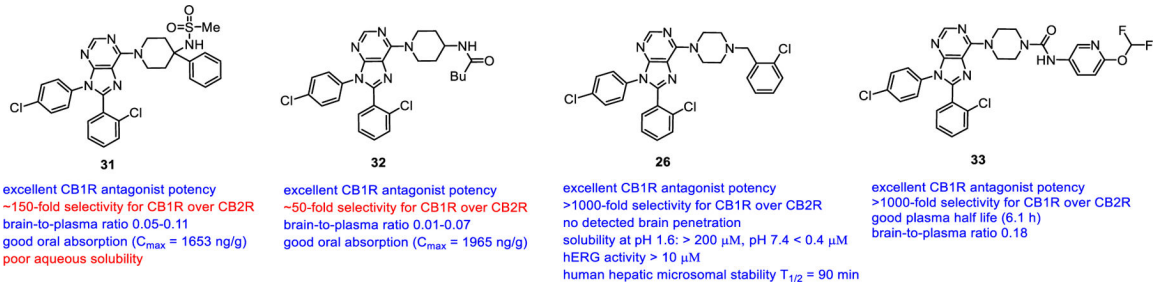


Fig. (6).

Structures of purine-based peripherally restricted CB1R inverse agonists developed by the Maitra group.

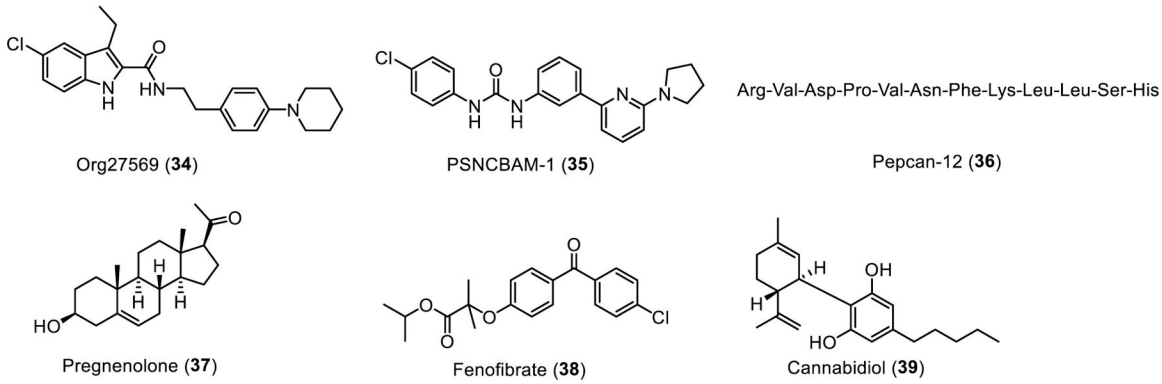
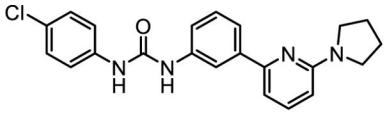


Fig. (7).
Structures of reported CB1R NAMs.



PSNCBAM-1 (**35**)

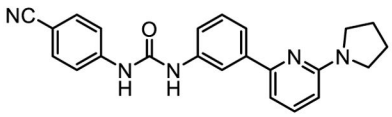
Ca^{2+} assay IC_{50} = 32.5 nM

GTPγS assay IC_{50} = 115 nM

[^{3}H]CP55,940 binding EC_{50} = 167 nM

[^{3}H]CP55,940 B_{max} = 4.53 pmol/mg

Rat liver microsomes $T_{1/2}$ = 13 min

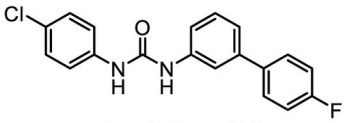


RTICBM-28 (**40**)

Ca^{2+} IC_{50} = 33 nM

[^{3}H]CP55,940 binding EC_{50} = 55 nM

Reduced THC's potency in drug discrimination test



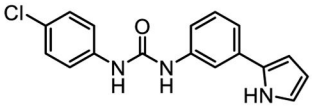
RTICBM-74 (**41**)

Ca^{2+} assay IC_{50} = 23 nM

GTPγS assay IC_{50} = 151 nM

Rat liver microsomes $T_{1/2}$ > 300 min

more effective than PSNCBAM-1 in the reinstatement of cocaine re-seeeking behavior



RTICBM-229 (**42**)

Ca^{2+} assay IC_{50} = 169 nM

GTPγS assay IC_{50} = 40 nM

[^{3}H]CP55,940 B_{max} = 5.87 pmol/mg

Fig. (8).

Structures of diarylurea-based CB1R PAM-Antagonists.