REVIEW

Blocking the Cannabinoid Receptors: Drug Candidates and Therapeutic Promises

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The CB_1 and CB_2 cannabinoid receptors have been described as two prime sites of action for endocannabinoids. Both the localization and pharmacology of these two G-protein-coupled receptors are well-described, and numerous selective ligands have been characterized. The physiological effects of *Cannabis sativa* (cannabis) and a throughout study of the endocannabinoid system allowed for the identification of several pathophysiological conditions – including obesity, dyslipidemia, addictions, inflammation, and allergies – in which blocking the cannabinoid receptors might be beneficial. Many CB_1 receptor antagonists are now in clinical trials, and the results of several studies involving the CB_1 antagonist lead compound rimonabant (**SR141716A**) are now available. This review describes the pharmacological tools that are currently available and the animal studies supporting the therapeutic use of cannabinoid receptor antagonists and inverse agonists. The data available from the clinical trials are also discussed.

1. Introduction. – Cannabis from *Cannabis sativa* has been used for both recreational and therapeutic purposes for several millennia. This widespread and long use allowed for the progressive collection of a large knowledge on the pharmacological properties of its constituents, which act on both the CB_1 and CB_2 cannabinoid receptors. The effects described for *C. sativa* mirror, at least in part, the effects obtained following the activation of these two G-protein-coupled receptors. Along these lines, the euphoric state obtained upon intake of cannabis is also observed following Δ^9-tetrahydrocannabinol (THC) administration, but is absent in animal models lacking the CB_1 cannabinoid receptor [1][2]. Similarly, the immunomodulatory effects of *C. sativa* (and of THC) are mediated by the CB_2 receptor, but are absent after administration of THC to mice lacking this receptor [3].

After the identification of the two cannabinoid receptors [4][5], the reported effects of *C. sativa* and of THC constituted a powerful incentive in developing agents that are able to block these receptors. Additional insight into the potential of such therapeutic approach was gained by obtaining mice lacking one [1–3] or both [6] cannabinoid receptors. For example, CB_1 knockout mice eat less [7] and are leaner [8]

compared to the corresponding wild-type mice. They are also less prone to acquire addictions [1][9] [10] and have reduced withdrawal symptoms [1].

A decade and a half after the description of the diarylpyrazole rimonabant (**SR141716A**; see *Fig. 1* below), the first potent and selective CB_1 antagonist [11], two prime applications of CB_1 antagonists are close to enter clinic: the treatment of obesity and metabolic syndrome, as well as the treatment of addictions. Regarding the CB_2 receptor, much less is known, even though the first antagonists, the pyrazole **SR144528** (see *Fig. 4* below), was described almost ten years ago [12]. The strong expression of the receptor by immune cells, both in the periphery and in the central nervous system (CNS) predicts that modulation of inflammations or allergies could be achieved with appropriate CB_2 receptor antagonists.

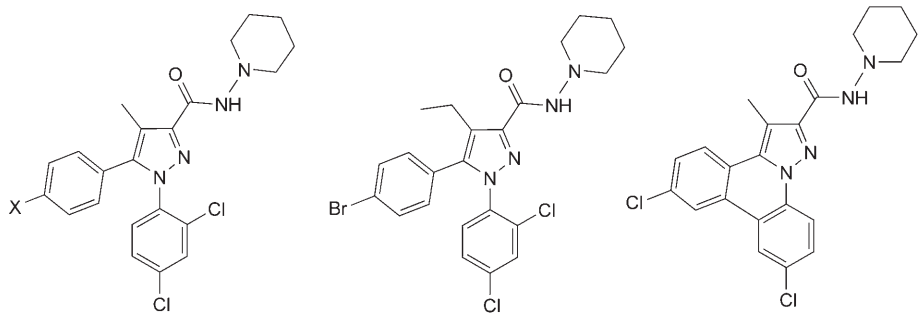
Due to the abundance of reviews dealing with this subject, this review article focuses only on compounds and applications close to the clinic or, at least, strongly supported by preclinical data.

2. Blocking the CB_1 Cannabinoid Receptor. – 2.1. *Pharmacological Tools.* The compound **SR141716A**, also known as rimonabant (*Acomplia*®; *Fig. 1*), was the first cannabinoid-receptor blocker showing high potency and selectivity for the CB_1 receptor. Developed at *Sanofi-Recherche*, and described in the scientific literature in 1994–1995 as a CB_1 antagonist [11][13], the pharmacology and medicinal chemistry of **SR141716A** have been extensively studied. Rimonabant is now described as an inverse agonist at the CB_1 cannabinoid receptor, displaying negative intrinsic activity in both heterologous and constitutive systems (for a review, see [14]). Its affinity for the CB_1 receptor lies in the range 1–20 nM, depending on the studies, its affinity for the CB_2 receptor being in the micromolar range. Rimonabant potency, selectivity, and oral bioavailability made it a good pharmacological tool, as well as a promising drug candidate.

The chemical structure of rimonabant allowed for some straightforward medicinal-chemistry studies such as modulating the substituents on the aryl rings and both the type and position of the residues at the pyrazole moiety. Albeit these studies did not result in striking improvements of the affinity for the CB_1 receptor, they allowed for a better understanding of rimonabant interactions with the receptor.

Along these lines, the different CB_1 receptor models developed, as well as mutation data showed that K3.28 is a direct interaction site for rimonabant derivatives [15–17], and that F 3.36 and W5.43 are also part of the binding site [18]. These models were also used as a molecular basis to rationalize the reported inverse-agonistic activity of rimonabant [15] (for a review, see [19]).

The compound **AM251** (*Fig. 1*) is a close analogue of rimonabant, only differing by the exchange of an I-atom for a Cl-atom on the 5-phenyl ring [20][21]. Numerous studies were conducted with **AM251**, which has a similar affinity and functionality as rimonabant. Of interest, however, are some studies showing differences in the effects of the two inverse agonists. For example, studies on GABAergic and glutamatergic transmission in the *hypothalami* of both wild-type and $CB_1^{-/-}$ knockout mice suggested that **AM251** is more selective compared to rimonabant, which kept some activity in the knockout tissues [22–25]. This could be particularly relevant, especially when looking at the pharmacology of the additional cannabinoid receptors [26].



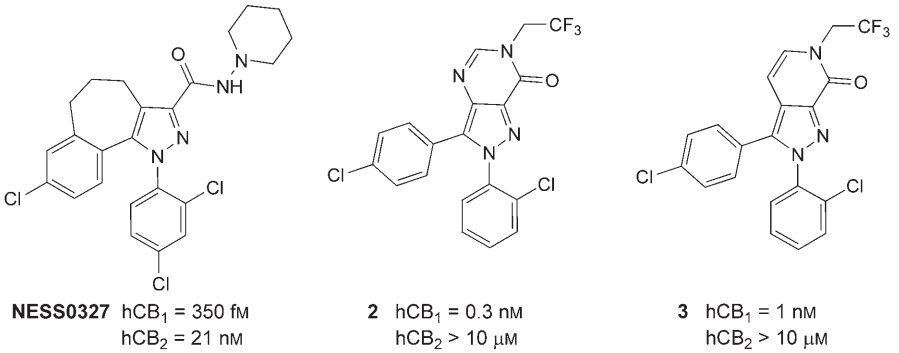


Fig. 1. *Structures and cannabinoid receptor affinities of rimonabant* (**SR141716A**) *and related antagonists.* hCB: human cannabinoid receptor; rCB: rat cannabinoid receptor.

Together, the two pyrazole derivatives **SR141716A** and **AM251** allowed for a better understanding of the endocannabinoid system, and constituted optimal tools in exploring the therapeutic potential of modulating the CB_1 receptor.

Another pyrazole derivative closely related to rimonabant, **SR147778** (*Fig. 1*), was described as a potent, orally active antagonist/inverse agonist of the CB_1 receptor. It possesses very similar pharmacological properties in terms of affinity and functionality [27] as the lead compound rimonabant, and to date, no differences were reported when used in *in vivo* models [28–30].

More recently, several series of conformationally constrained derivatives mimicking the rimonabant structure have been described. The aim was to improve the pharmacology of rimonabant by blocking the compound structure in its putative active conformation [31]. Several strategies were applied, *e.g.*, blocking the rotation of the phenyl rings (*e.g.*, **1** or **NESS0327**) or that of the acyl function at C(3) (*e.g.*, **2** or **3**), which gave rise to a series of compounds differing by the nature and position of the linking elements [32][33]. Enhanced affinity or selectivity for the CB_1 receptor were

described for some of these derivatives [34][35], **NESS0327** showing the most dramatic improvement, with a reported affinity of 350 fM (350×10^{-15} M) [36]. Note that a contrasting report exists concerning the affinity of this compound [37]. More-extensive studies are needed to determine whether these constrained analogues will prove to be superior to rimonabant when used *in vivo*.

Isosteric replacement of the pyrazole moiety is another avenue that was thoroughly studied (for reviews, see [32][33]). As shown in *Fig. 2*, either five-membered central moieties (imidazoles; *e.g.*, **4**–**6**) [38][39], triazoles (*e.g.*, **LH-21**, **7**, **8**) [38–40], thiazoles [39], or congeners with six-membered central moieties such as phenyl rings (*e.g.*, **O-1803**) [41] or pyridines (*e.g.*, **9** and **10**) [42][43] were prepared to maintain the critical substituents – *i.e.*, the substituted phenyl rings and a lipophilic moiety connected through a H-bond acceptor – in the correct conformation [32]. Along those lines, the structure–activity relationships (SAR) found for the imidazole derivatives were similar to those described for the pyrazole derivatives, the later being also active *per os* [38][39][44]. Note, that further chemical-optimization efforts of these isosteres led to additional drugs (*e.g.*, the 1,8-naphthyridinone **11**) [45] that bind to the CB_1 receptor.

Besides the above pyrazole derivatives and their isosteres, diarylpyrazolines are a class of CB_1 receptor inverse agonists that could play an important role as modulators of the endocannabinoid system. The lead compounds of this class, **SLV319** and **SLV326** (*Fig. 3*), were developed at *Solvay Pharmaceuticals* [46][47]. They show affinities in the nanomolar range for the CB_1 receptor, as well as good selectivity and oral bioavailability. Antagonists not based on a *cyclic* central moiety were also developed [48], an excellent illustration of this class of compounds being *Merck*'s **MK-0364** (*Fig. 3*). The efforts leading to the characterization of this drug were recently reported [49], and the compound is now in clinical trials for treating obesity. Two other CB_1 receptor antagonists/inverse agonists currently in clinical trials should also be mentioned, although their structures have yet to be fully disclosed: *Pfizer*'s **CP-945,598** and *Sanofi-Aventis*' **Ave1625** (structures not shown).

Far from being comprehensive, this short overview attests of the large diversity of compounds acting as CB_1 receptor blockers, as reviewed previously [32][33]. Besides providing invaluable tools for the ongoing exploration of the endocannabinoid system, some of them already do or probably will constitute promising drug candidates, as described in the next section.

2.2. *Drug Candidates and Therapeutic Promises.* Rimonabant was used in numerous animal models to decipher either the role of the endocannabinoid system or the therapeutic promises of the CB_1 receptor antagonist. Actually, much of the groundbreaking research was done using **SR141716A**, which has the advantage of being selective and bioavailable orally. However, one should bear in mind that rimonabant displays some effects also in CB_1 knockout mice, suggesting additional pharmacological targets for this drug (see, *e.g.*, [22]).

Emerging from *in vivo* studies involving CB_1 receptor antagonists (*Table 1*), two main applications are reaching the clinic: treatment of obesity and metabolic syndrome, and treatment of addictions [50][51]. Indeed, for these two applications, quite consistent results have been obtained across studies and models. Unfortunately, in other areas of research, we are dealing with more-variable data, suggesting that

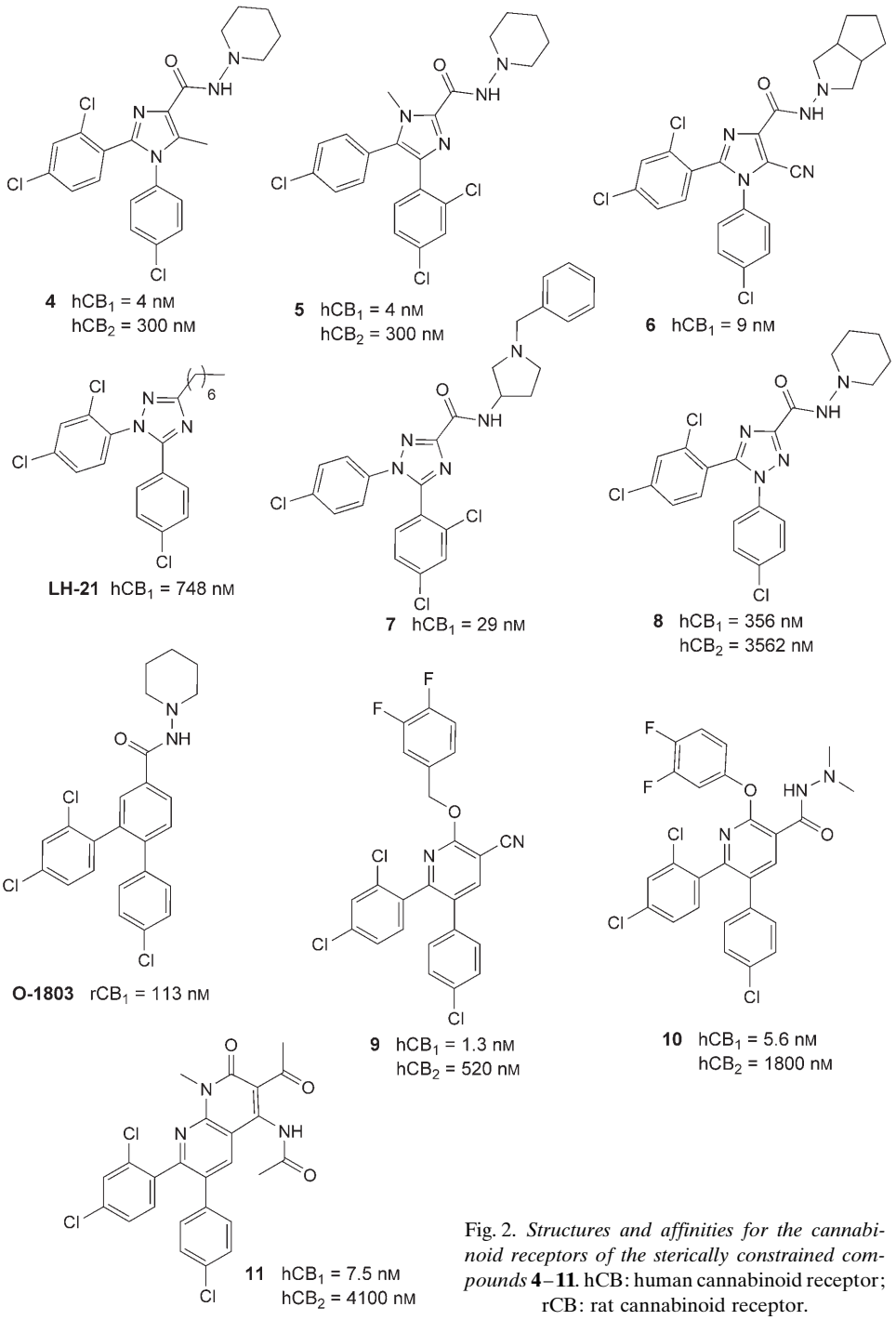
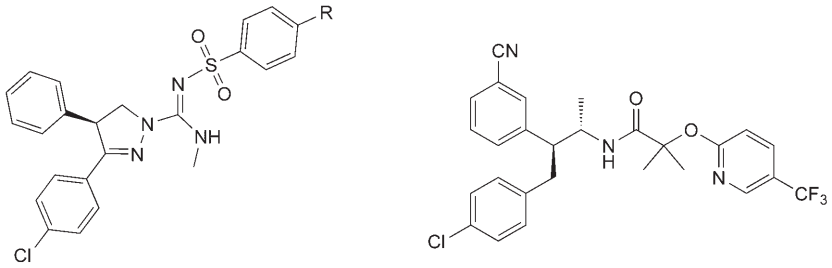


Fig. 2. *Structures and affinities for the cannabinoid receptors of the sterically constrained compounds* **4**–**11**. hCB: human cannabinoid receptor; rCB: rat cannabinoid receptor.



SLV319 R = Cl hCB_1 = 8 nM
hCB_2 = 7943 nM
SLV326 R = CF_3 hCB_1 = 36 nM
hCB_2 = 3515 nM

MK-0364 hCB_1 = 0.3 nM
hCB_2 = 290 nM

Fig. 3. *Structures and cannabinoid receptor affinities of two CB_1 receptor inverse agonists*

additional investigations will be necessary to, possibly, progress towards applications such as treatment of *Alzheimer*'s disease, schizophrenia [52], or memory loss.

2.2.1. *Treatment of Obesity and Metabolic Syndrome.* 2.2.1.1. *Animal Models.* Administration of **SR141716A** to animals results in decreased food consumption and reduced body weight. Albeit early results showed a selective effect for high-palatable food [53][54], similar effects were since obtained with both high-palatable and regular food [55][87][88]. Rimonabant-induced reduction in food intake is observed in lean as well as in genetically and diet-induced obese animals. The effect of the drug is even more striking when considering its effectiveness in food-restricted animals [87][89]. Importantly, neither water intake nor locomotion was affected by doses effective in inducing weight reduction. Potentially disappointing, the rapid development of tolerance to **SR141716A** anorectic effect was counterbalanced by the observed more-sustained reduction in body weight. However, following treatment discontinuation, the body weight returns to the levels of the untreated animals [55][59]. Besides the selectivity of rimonabant, its absence of effect in mice lacking the CB_1 receptor confirmed the CB_1 mediated mechanism of action [7][61][90]. Accordingly, administration of **AM251** resulted in similar data, confirming that the effect on weight reduction is a common feature of CB_1 antagonists [62][74][91], including less closely related compounds, *e.g.*, **LH-21** (*Fig. 2*) [58] or **MK-0364** (*Fig. 3.*) [49].

Subsequent studies highlighted the interactions between the CB_1 receptors, its endogenous ligands, and both orexigenic and anorexigenic mediators. Endocannabinoid levels are higher in the *hypothalamus* of genetically obese animals, which possess a deficient leptin system. Accordingly, injection of the neurohormone leptin results in decreased endocannabinoid levels in the *hypothalamus* [7]. They also vary along the nutritional status, for example increasing in the limbic forebrain of food-deprived rats, while the hypothalamic levels of 2-arachidonoylglycerol (2-AG) are decreased upon feeding [92].

In addition to leptin, several other mediators (*Table 2*) were suggested to play a role in the endocannabinoid-mediated control of food intake and energy expenditure (for recent reviews, see [93][94]). Along this line, hypothalamic CB_1 receptor mRNA was

Table 1. *Selected Studies Involving CB_1 Receptor Antagonists in Animal Models*

Antagonist	Model	Output	Ref.
SR141716A	mouse	food intake	[53]
SR141716A	marmoset	food intake	[54]
SR141716A	rat	food intake	[55]
SLV-319, **SR141716A**	rat	food intake	[56]
SR147778	rat	food intake	[27]
AM251	rat	food intake	[57]
LH-21	rat (fa/fa)[a])	food intake and body weight	[58]
SR141716A	rat (fa/fa)	food intake and body weight	[59][60]
SR141716A	mouse (DIO)[b])	food intake and body weight	[61]
AM251	mouse (DIO)	food intake and body weight	[62]
SR141716A	mouse-$CB_1{}^{-/-}$	food intake	[7]
SR141716A	mouse	EtOH intake	[53]
SR141716A	rat	EtOH intake	[63]
SR141716A	sP-rat[c])	EtOH intake	[64]
SR147778	rat	EtOH intake	[30]
AM251	rat	methamphetamine self-administration	[65]
SR141716A	rat	heroin self-administration	[66]
SR141716A	mouse	morphine self-administration	[66]
SR141716A	rat	nicotine self-administration	[67]
SR141716A	rat	nicotine-associated cues	[68]
SR141716A	rat & mouse	memory tasks	[69]
SR141716A	rat	memory tasks	[70]
SR141716A	rat	memory tasks	[71]
AM251	mouse (WT & $CB_1{}^{-/-}$)	anxiety models	[25]
AM251	mouse	anxiety models	[72]
SR141716A	mouse	anxiety models	[73]
AM251	mouse	anxiety models	[73]
AM251	mouse	anti-depression tests	[74]
SR141716A	rat	schizophrenia model	[75]
SR141716A	monkey	schizophrenia model	[45]
SR141716A	rat (reserpine treated)	*Parkinson* models	[76]
SR141716A	rat (6-OH-DOPA treated)	*Parkinson* models	[77]
SR141718	rat	acetylcholine release (*hippocampus*)	[78–80]
SR141718	rat & mouse	acetylcholine release (*hippocampus*)	[80]
AM251	rat & mouse	acetylcholine release (*hippocampus*)	[80]
SR141718	rat	acetylcholine release (medial prefrontal *cortex*)	[81]
SR141716A	rat	penile erection	[82]
SR141716A	mouse	liver fibrosis	[83]
SR141716A	rat & mouse	small-intestine inflammation	[84]
SR141716A	rat	neuropathic pain	[85]
SR141716A	rat (lean and DIO)	arthritic pain and inflammation	[86]

[a]) Leptin-receptor-deficient *Zucker* rat. [b]) Diet-induced obese. [c]) Sardinian alcohol-preferring rats.

found to be co-expressed with neuropeptides known to modulate food intake [8]. These studies underscore the complexity of the mechanisms involved, but also open additional therapeutic avenues in combining CB_1 receptor antagonists with drugs

acting on selected orexigenic/anorexigenic mediators. Some combinations – *e.g.*, a CB_1 receptor antagonist with a MCH receptor antagonist – are described in the patent literature as having synergistic effects [95] (for a review, see [33]). However, the advantage of such combinations over single-target strategies remains to be proven.

Table 2. *Interaction of the Endocannabinoid System with Anorexigenic and Orexigenic Factors*

Mediator	Action	Ref.[a])
Leptin	upregulates anorexigenic and downregulates orexigenic neuropeptides, resp.	[7][90]
NPY	increases food intake	[7][96]
Ghrelin	increases food intake *via* activation of the growth hormone-secretagogue receptor	[97–99]
Orexin	implicated in food intake in satiated rats	[100][101]
Endogenous opioids	increases food intake	[102][103]
CRH[b])	inhibits food intake	[8][104]
α-MSH[c])	suppresses food intake *via* activation of the melanocortin receptor 4 (MCR4)	[105]
CART[d])	the peptide product of CART is a tonically active anorectic mediator	[8][106]

[a]) References linking each mediator to the endocannabinoid system. [b]) Corticotropin-releasing hormone. [c]) α-Melanocyte-stimulating hormone. [d]) Cocaine- and amphetamine-related transcript.

At least two lines of evidence – the observation that weight loss is maintained even when the effect on food intake has faded [55][61][62], and the fact that treated adult animals have a lower body weight compared to paired-fed animals [8][61] – suggested that CB_1 receptor antagonists have peripheral effects beyond their CNS-mediated action. This is further supported by CB_1 knockout mice, which did not respond to diet-induced obesity, and by their lean phenotype compared to wild-type littermates for a similar caloric intake (when comparing the caloric intake reported to their body weight) [90][107].

Prime peripheral sites of action for CB_1 receptor antagonists are the adipocytes and the liver. Adipocytes express functional CB_1 receptors, whose activation results in increased lipoprotein lipase activity (and, thus, increased lipogenesis) and reduced adiponectin expression [8][59]. Adiponectin (or Acrp30) is a plasma protein, exclusively secreted by adipocytes, known to induce free fatty acid (FFA) oxidation, as well as hyperglycemia and hyperinsulinemia reduction. Rimonabant-treated genetically obese rats (fa/fa) have a reduced body-weight, express higher levels of adiponectin, and have a reduced hyperinsulinemia compared to control obese animals [59][108]. Similar results are obtained in diet-induced obese (DIO) mice [109]. Moreover, the high cholesterol levels and low HDLc/LDLc ratio found in DIO mice were improved [109], and the adipocyte morphology was restored (*i.e.*, a reduction in size and volume took place) upon rimonabant treatment [110]. A comparison of the adipocytes transcriptional profile from DIO and control mice showed that rimonabant was able to revert the changes in adipocytes gene expression induced by obesity, resulting in enhanced lipolysis, increased energy expenditure, and improved control of glucose homeostasis [110]. A recent study by *Gary-Bobo et al.* [111] also showed that

rimonabant inhibits adipocytes proliferation and increases their maturation, without inducing accumulation of lipids.

The liver is another peripheral organ relevant to lipid metabolism, where CB_1 receptor expression is found [83][107]. Activation of hepatocytes CB_1 receptors results in enhanced expression of SREBP-1c, a lipogenic transcription factor, and of its targets Ac-CoA carboxylase-1 and fatty acid synthase (FAS). Since those two enzymes are involved in fatty acid synthesis, blocking the CB_1 receptor, thus decreasing SREBP-1c expression, results in decreased *de novo* fatty acid synthesis [107]. Strikingly, a high fat diet upregulates CB_1 receptor expression in mice, increases anandamide levels (by reducing FAAH activity), and increases the rate of fatty acid synthesis, a mechanism responsible for the fatty liver found in wild-type, but not in $CB_1^{-/-}$ mice fed with high-fat food [107]. *Osei-Hyiaman* and colleagues [106][107] also found a similar CB_1 mediated increase in SREBP-1c and FAS expression in the *hypothalamus*, where rimonabant blocks the expression increase of SREBP-1c and FAS in a fasted/re-fed paradigm. FAS inhibitors are known to reduce food intake [112][113], suggesting that the reduction of hypothalamic FAS expression by rimonabant could be an additional mechanism explaining its effects on food intake.

2.2.1.2. *Clinical Studies.* Several CB_1 receptor antagonists are in clinical trials for the treatment of human obesity and/or metabolic syndrome, including *Sanofi-Aventis*' **SR141716A**, **SR147778**, and **Ave1625**, *Solvay*'s **SLV319**, *Pfizer*'s **CP-945,598**, and *Merck*'s **MK-0364**. To date, the majority of the reported Phase-III clinical-trial data are those gathered during the studies involving rimonabant (the so-called 'Rimonabant In Obesity' (RIO) studies) [114]. Besides, small-scale studies with 60–80 participants allowed for the description of an upregulated peripheral endocannabinoid system in obese, when compared to lean subjects [115][116]. Mature adipocytes of obese subjects are characterized by reduced CB_1 receptor and FAAH expression, and higher levels of circulating arachidonoyl ethanolamide (AEA) and 2-arachidonoylglycerol (2-AG). A subsequent study found a correlation between these modifications of the endocannabinoid system and visceral (abdominal) fat mass [116]. Interestingly, the modifications found in the obese subjects were maintained following a 5% weight-reduction obtained by reducing caloric intake [115].

The results of four RIO studies, with an overall enrolment of *ca.* 6,600 obese ($BMI > 30$)[1]) or overweight ($BMI > 27$) subjects, were recently published (*Table 3*). In addition to body weight, dyslipidemia or hypertension were among the inclusion criteria for the 'RIO Lipids' studies performed in Europe and North America [117–119]. In the 'RIO Diabetes' study, obese and overweight subjects with type-II diabetes, inadequately controlled by metformin or sulfonylurea, were enrolled [120]. Rimonabant was administered at 5 or 20 mg/d, in conjunction with a hypocaloric diet (deficit of 600 kcal/d), and compared to placebo in randomized, double-blind trials. In all four studies, weight and waist circumference, a sign of visceral obesity, were significantly reduced in the group treated daily with the 20-mg dose, as compared to the placebo group. Lipid variables were also improved, with reduced triglycerides levels and increased HDL levels. Plasmatic adiponectin levels were increased by the treatment, whereas those of leptin were reduced. In the 'RIO North America' trial, subjects were

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[1]) *BMI* refers to body-mass index.

Table 3. *Reported or Published Clinical Trials with Rimonabant*. All the changes were statistically significant compared to placebo, except those marked with asterisks (*)

Denomination	N[a])	Condition (BMI)[1])	Treatment and duration	Results[b])					
				Weight [kg]	Waist [cm]	HDL [%][c])	TGc [%][c])	Glc[d])	Ins[e])
RIO Lipids [117]	1,036	dyslipidemia (BMI 27–40)	placebo *vs.* rimonabant (5 or 20 mg/d; 1 year)	−5.4	−4.7	8.1	−12.4	−0.03*	−2.6
RIO Europe [118] (NCT00386061)	1,507	hypertension and/or dyslipidemia (BMI >27)	placebo *vs.* rimonabant (5 or 20 mg/d; 1 year)	−4.8	−4.1	8.7	−13.6	−0.12	−2.8
RIO North America [119] (NCT00029861)	3,045	hypertension and/or dyslipidemia (BMI >27)	placebo *vs.* rimonabant (5 or 20 mg/d; 1 year) followed by re-randomization (1 year)	−4.7[f])	−3.6[f])	7.2[f])	−13.2[f])	−0.65*[f])	−2.8[f])
RIO Diabetes [120] (NCT00029848)	1,045	uncontrolled type-II diabetes (BMI>27)	placebo *vs.* rimonabant (5 or 20 mg/d; 1 year)	−3.9	−3.3	8.3	−16.4	−0.97	−1.1*
SERENADE [121] (NCT00257257)	278	type-II diabetes previously untreated	placebo *vs.* rimonabant (20 mg/d; 6 months)	For a HbA_{1c} baseline level of 7.9%: reduction of 0.8% (placebo: 0.3% reduction) For a HbA_{1c} baseline level >8.5%: reduction of 1.9% (placebo: 0.7% reduction)					
STRATUS-US [153] (NCT00358228)	787	smokers (>10 cigarettes/day, average 23) motivated to quit	placebo *vs.* rimonabant (5 or 20 mg/d; 10 weeks, further evaluation after 1 year)	• Smoking abstinence at 10th week: 27.6% (placebo: 16.1%) • Smoking abstinence at 1 year: 36.2% (placebo: 20.6%) • Weight gain of 0.6 kg (placebo: 3.7 kg)					

[a]) Number of subjects tested. [b]) Placebo-subtracted changes for the group receiving rimonabant (20 mg/d). [c]) Relative to baseline. [d]) Fasting glucose concentration (in mM). [e]) Fasting insulin (mU/ml). [f]) Results for the group receiving rimonabant at a dose of 20 mg/d over 1 year.

re-randomized at the end of the first year of treatment, allowing for both the study of a two-year treatment with rimonabant (20 mg/d) and of the consequences of treatment discontinuation [119]. Subjects re-assigned to placebo after one year of rimonabant regained weight and ended the two-year trial with the same weight than the subjects who had received two years of placebo. A similar phenomenon was reported for the waist circumference, and for the triglycerides and HDL levels, suggesting that long-term treatment is needed to maintain reduced weight and improved cardiometabolic-risk factors.

In the 'RIO Diabetes' study, the enrolled subjects had uncontrolled type-II diabetes, despite their antidiabetic drugs metformin or sulfonylurea, with glycosylated haemoglobin (HbA_{1c}) levels of 6.5–10%, reflecting the poor effect of their antidiabetic treatment. Following one year of rimonabant treatment, HbA_{1c} levels were significantly reduced (−0.7%), as were the fasting glucose concentrations (−0.97 mmol/l).

Finally, the results of the so-called SERENADE (study evaluating rimonabant efficacy in drug-naive diabetic) trial, involving 278 subjects with type-II diabetes not currently treated with any antidiabetic drug, were recently presented [121]. The primary outcome of the study was the absolute change in HbA_{1C} from baseline (7.9%) to month six. A reduction of 0.8% was achieved in the rimonabant group treated with 20 mg/d, compared to a reduction of 0.3% in the placebo arm. In addition, 50% of the subjects in the rimonabant arm achieved the *American Diabetes Association* HbA_{1c} value of 7% [121]. As for the other studies, weight (−4 kg compared to placebo) and waist circumference (−3.7 cm compared to placebo) were reduced, and serum lipid profile improved significantly compared to placebo [121]. The complete results of this trial have yet to be published.

Nausea (*ca.* 12% for rimonabant and 5% for placebo), dizziness (*ca.* 9% for rimonabant and 5% for placebo), diarrhea (*ca.* 7% for rimonabant and 4% for placebo), and vomiting (*ca.* 6% for rimonabant and 2% for placebo) were the adverse effects more frequently reported for rimonabant, compared to placebo, during the RIO studies. Due to rimonabant activity at the CB_1 receptor and its extensive passage through the blood–brain barrier, fear existed concerning its potential adverse effect on mood or locomotion. During the RIO studies, no major differences were reported in the anxiety and depression scores between rimonabant and placebo groups, suggesting that blockade of the CB_1 receptor by rimonabant had no CNS overt effects [117–120]. However, patients with severe psychiatric disorders or receiving antidepressants were excluded from the RIO trials, mitigating this good result. Finally, discontinuation of the treatment due to nausea, diarrhea, dizziness, anxiety, and depression were more frequent in rimonabant groups compared to placebo.

Taken together, these results, demonstrating the efficacy and safety of rimonabant in treating obesity and dyslipidemia, are encouraging not only for this specific lead, but possibly for all CB_1 antagonists. It remains to be seen if the same efficacy and tolerability can be obtained in large-scale population, where the incidence of polymedication and psychiatric disorders are higher than in the study groups. In 2006, rimonabant received from the *European Medicines Agency* a marketing authorization for the European Union as '*an adjunct to diet and exercise in the treatment of overweight or obese patients with associated risk factors such as type-II diabetes or dyslipidemia*'.

2.2.2. *Treatment of Addictions.* 2.2.2.1. *Animal Models.* Cannabinoid receptors are highly expressed in the brain reward circuitry. In addition, it was shown that, in the mesolimbic system, interactions exist between the endocannabinoid system and dopamine [122–124]. Accordingly, the CB_1 receptor is known to modulate some of the rewarding properties of food [53][64] and of alcohol, nicotine, and drugs of abuse (for a review, see [125]). Animal models reproducing the addictive properties seen in humans are well-described [126][127] and, when used in conjunction with CB_1 antagonists and/or knockout animals, allow for a better understanding of the role of CB_1 receptors in addictions [125][128][129]. For instance, the addictive effects of morphine [1][10], nicotine [130], and alcohol [122][131] are reduced in knockout animals. On the other hand, administration of rimonabant resulted in decreased morphine [66], nicotine [67][132], or alcohol [53][63] self-administration in rodents, suggesting that, indeed, modulation of the endocannabinoid system can be used to treat addictions (see *Table 1* above).

When administered to rats, rimonabant decreases nicotine self-administration and nicotine-induced dopamine release in the *nucleus accumbens* (an important structure of the brain reward circuit) [67], blocks the expression of nicotine-induced conditioned place preference [129][133], and attenuates the reinstatement of nicotine seeking [132]. Rimonabant efficacy in these models suggests that it could be used as smoking cessation aid by decreasing the rewarding properties of nicotine. Smoking-associated environmental stimuli, mimicked in the animal by resistance to extinction of drug-seeking behavior elicited by nicotine-associated cues [134], are thought to be an important obstacle in quitting smoking [135–137]. Rats trained to self-administer nicotine in the presence of an environmental stimulus maintain their drug-seeking behavior for months when the stimulus is presented in the absence of nicotine [68]. In those rats, rimonabant was able to reduce the response maintained by nicotine-associated cues in the absence of nicotine, suggesting that the drug could be useful in maintaining abstinence following smoking cessation [68]. Similarly to their action on nicotine self-administration, CB_1 receptor antagonists reduced ethanol intake in various experimental paradigms [27][53][63][131][138]. Rimonabant also reduced the motivation to consume alcohol [64][139], and prevented the acquisition of drinking behavior in alcohol-preferring rats (sP-rats) [140]. Of interest is also the ability of CB_1 receptor antagonists to suppress the alcohol-deprivation effects in sP-rats [141], and the absence of withdrawal syndrome in CB_1 receptor knockout mice [142]. Both the effects of rimonabant on smoking cessation and alcoholism are currently under study in clinical trials (see next section).

Besides alcohol and nicotine, rimonabant modulates the effects of other drugs of abuse like cocaine and opiates. Indeed, cocaine [143], heroin [40][66], and morphine [66] self-administration are attenuated by rimonabant administration. Interestingly, acute administration of rimonabant precipitates withdrawal in opiate-dependent animals [144]. However, when rimonabant was administered for several days to opiate-dependent animals, it reduced the magnitude of naloxone-induced withdrawal, suggesting that it could be potentially suitable in ameliorating opiate withdrawal [145][146].

Almost 20 years ago, *Di Chiara* and *Imperato* [147] showed that drugs of abuse, despite different modes of action, increase synaptic dopamine concentrations in the

mesolimbic system [147]. More recently, fluctuations in dopamine levels were shown to occur during reward seeking [148][149], and different patterns of fluctuations were observed, depending on the drug of abuse involved [150]. *Cheer et al.* [150] recently showed that rimonabant was able to attenuate dopamine fluctuations induced by nicotine, alcohol, and cocaine, despite their different patterns, offering a good rationalization for its *in vivo* efficacy in treating different types of drug abuse [150]. This further supports the role of CB_1 receptor antagonists as a unique treatment for multiple addictions.

2.2.2.2. *Clinical Studies.* The quite impressive results obtained with animal models granted further evaluation of rimonabant in treating addictions in human. Although complete results of such Phase-III trials have yet to be published, some results were presented during meetings.

Studies with rimonabant and tobacco use (STRATUS) were designed to assess the potential of the drug as a help to smokers motivated to quit (*Table 3*). The STRATUS studies involved an overall of 7,164 subjects, divided in three short-term studies (STRATUS-US, STRATUS-EU, and STRATUS-META) and one medium-term study (STRATUS-WW) [114][151][152]. The results of the STRATUS-US trial were presented in 2004. In this study, 787 subjects smoking ten or more cigarettes per day, and wanting to stop smoking, received rimonabant (5 or 20 mg/d) or placebo for ten weeks, and were asked to quit smoking at day 15 of the study. At the end of the treatment, a significantly higher proportion of subjects (27.6%) in the rimonabant (20 mg/d) arm had indeed quit smoking compared to the placebo group (16.1%). At one year off drug, there was still a significantly higher proportion of abstinence in the rimonabant group [153].

In the STRATUS-WW study, 5,000 subjects received rimonabant (5 or 20 mg/d) for ten weeks, after which abstinent smokers were re-randomized into placebo and rimonabant (5 or 20 mg/d) arms for an additional 42 weeks, to study the antirelapse properties of the drug [152]. A 10% difference in favor of rimonabant (5 and 20 mg/d) was obtained for maintenance of the abstinence at week 52, corresponding to a 30% reduction in the odds of relapsing [152]. The later data suggest that prolonged treatment could be more powerful in helping smokers on the long term, since fewer subjects relapsed in the 20 mg/20 mg and 20 mg/5 mg groups than in the 20 mg/placebo group. However, both the time-course of the treatment and the dose needed for help maintaining abstinence are still unclear at this point.

The potential of treating alcoholism using rimonabant is currently studied in a Phase-II clinical trial sponsored by the U.S. *National Institute on Alcohol Abuse and Alcoholism* (NCT00075205). The study is recruiting alcoholic subjects who will receive rimonabant or placebo for a two-week period, before evaluating their alcohol self-administration.

The future will show if additional CB_1 antagonists will be tested as potential treatment for smokers, and if addictions to drugs of abuse could be efficiently treated by these compounds.

2.2.3. *Treatment of Liver Fibrosis.* Chronic insults to the liver result in liver fibrosis, and eventually in cirrhosis. Cannabinoid CB_1 and CB_2 receptors are expressed in the human liver, and are upregulated under cirrhotic conditions [83][154]. In addition, regular cannabis smoking in patients with chronic hepatitis C was correlated with an

enhanced development of liver fibrosis, suggesting the presence of a link between cannabinoid system and liver fibrosis [155]. While the CB_2 receptor was shown to posses antifibrogenic properties [154], the use of CB_1 knockout mice revealed a markedly reduced fibrosis progression compared to wild-type mice in three models of chronic liver injury. Indeed, reduced matrix remodeling and decreased fibrogenic response, through growth inhibition and increased apoptosis of hepatic myofibroblasts, were seen in knockout animals. Similar results were obtained with rimonabant through a CB_1 dependent mechanism, suggesting that the CB_1 receptor is a valuable target for treating liver fibrosis [83].

CB_1 Receptors were also implicated in the generalized vasodilatation associated with advanced cirrhosis [156][157]. An increased endocannabinoid tone was suggested to be responsible for the haemodynamic changes observed in the presence of cirrhotic conditions. Indeed, CB_1 receptor expression is upregulated in hepatic endothelial cells, and anandamide levels in monocytes are increased in liver cirrhosis [156]. These changes were reverted upon administration of rimonabant (**SR141716A**) [156] or **AM251** [158] to cirrhotic, but not control, rats.

Although not yet confirmed by clinical-trial data, the relevance of CB_1 receptor antagonists in treating liver conditions is supported by strong evidence. Indeed, rimonabant was effective in improving both earlier [83] and later stages [156][159] of the liver-cirrhosis pathology.

3. Blocking the CB_2 Cannabinoid Receptor. – 3.1 *Pharmacological Tools.* Similarly to what happened with the CB_1 receptor, the first selective CB_2 receptor antagonist, **SR144528** (*Fig. 4*), was developed around a pyrazole moiety at *Sanofi-Recherches* [12]. Analogously to rimonabant (**SR141716A**; *Fig. 1*), **SR144528** has been described both as an antagonist [12] and as an inverse agonist [160][161], probably due to the different experimental protocols used. In addition to **SR144528**, other pyrazole derivatives were reported to bind to the CB_2 receptor [33][162][163]. Interestingly enough, some constrained 1,5-diarylpyrazole derivatives, with high affinity and selectivity for the CB_2 receptor [35][164], were recently described as agonists rather than as antagonists [165].

Another often used CB_2 receptor antagonist is **AM630** (*Fig. 4*), which, like **WIN-55,212-2** (structure not shown), contains a fused indole moiety [166][167]. However **AM630** is less selective than **SR144528**. The indole derivative **WIN-55,212-3** (not shown), until recently described as the inactive enantiomer of **WIN-55,212-2**, was shown to act as an inverse agonist [168] or competitive antagonist [162] at the CB_2 receptor. Nevertheless, its low affinity (*ca.* 13 μM) and efficacy will probably limit its use as a CB_2 receptor antagonist/inverse agonist.

In 2001, *Japan Tobacco* described a new class of potent and selective CB_2 receptor ligands based on a quinoline carboxamide moiety [169]. **JTE-907** (*Fig. 4*) was further characterized, and showed high selectivity for the CB_2 receptor, with inverse-agonistic properties [170][171].

More recently, a new class of selective CB_2 receptor ligands based on a triaryl bis-sulfone backbone, exemplified by **Sch336** (*Fig. 4*), was developed at *Schering-Plough* [172][173]. Some SAR studies for these compounds, exhibiting inverse-agonistic properties at the CB_2 receptor, were also described. Interestingly, the same group

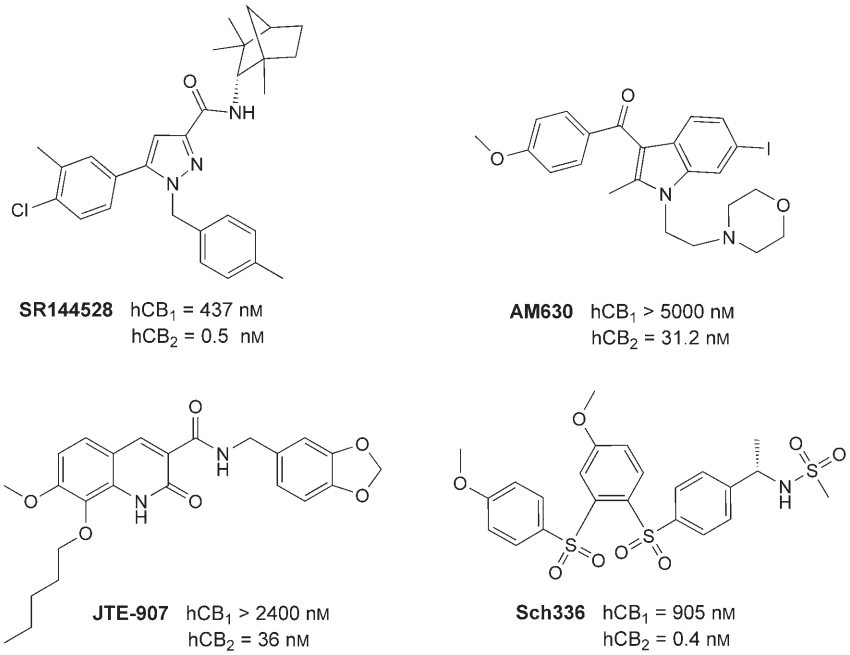

Fig. 4. *Structures and affinities of drugs recently investigated as antagonists or inverse agonist for the CB_2 cannabinoid receptor*

reported the synthesis and characterization of a [^{35}S]-radiolabeled form of **Sch336** ([^{35}S]-**SCH336**) [174].

It is apparent from this short description that, in contrast with the other class of cannabinoid-receptor ligands, and at least in the scientific literature, only few selective CB_2 receptor antagonists have been described so far. It is expected that their number will rise with further SAR studies for the CB_2 ligands (see, *e.g.*, [175–178], and, for a review, [179]). With more targeted research projects [162], the effects of blocking the CB_2 receptor will be better understood.

3.2. *Drug Candidates and Therapeutic Promises.* The CB_2 receptor is highly expressed throughout the immune system [180][181] and was more recently described in the SNC under both pathological [182] and physiological conditions [183]. This quite specific localization, as well as the characterization of CB_2 knockout mice [3], suggest that CB_2 receptor ligands would have potential therapeutic applications as immunomodulators. Several papers reported the role of the CB_2 receptor in modulating leukocytes migration [184–187], activation [188], and antigen processing [189]. Therefore, the *in vivo* studies involving CB_2 receptor antagonists were mainly conducted using inflammation and allergy models. Additional applications could arise from the studies on bone physiology. Indeed, some authors suggested that blocking the CB_2 receptor protects from bone loss in ovariectomized mice [190]. However, others showed that CB_2 receptor activation is involved in protecting from bone loss [191],

which suggests that further research is needed to unravel the role of this receptor in bone physiopathology.

3.2.1. *Modulation of Inflammation and Allergies.* Carrageenan injection in the hind paw is a common model to assess the anti-inflammatory properties of various compounds. In this model, administration of **SR144528** and **JTE-907** (*Fig. 4*) to mice dose-dependently reduced the carrageenan-induced paw edema, suggesting that blocking the CB_2 receptor results in anti-inflammation [170]. Alternatively, a topical irritant can be applied on the animal skin to study the effect of these compounds on cutaneous inflammation. For example, application of the irritant 12-*O*-tetradecanoyl-phorbol-13-acetate on mouse ear results in increased levels of 2-arachidonoylglycerol (2-AG), infiltration of neutrophils, and swelling; and topical application of **SR144528** reduces in a dose-dependent fashion swelling and infiltration by leukocytes [192]. Note that topical application of 2-AG [192], of noladin ether [193], or of the CB_2 selective agonist **HU-308** (structure not shown) [193] also results in ear swelling. These effects are blocked by oral administration of **SR144528** or **JTE-907**, suggesting that the CB_2 receptor is involved in local inflammation and that antagonists could prevent such processes.

A large body of evidence supports the role of CB_2 receptors in modulating immune-cell recruitment (for reviews, see [194–196]). A recent *in vivo* study demonstrated that the selective CB_2 inverse-agonist **Sch336** (*Fig. 4*) can modulate the migration of leukocytes towards implanted sponges soaked in the cannabinoid agonist **HU-210** (structures not shown) or the chemokine **CCL-2**. In addition, **Sch336** and **SR144528** decreased the recruitment of leukocytes in a mouse model of delayed-type hypersensitivity, as well as eosinophils in the bronchoalveolar lavage fluid in a mouse model of allergic asthma [197]. 2,4-Dinitrofluorobenzene-induced dermatitis in sensitized mouse is another model of allergic reaction resulting in an IgE-mediated triphasic cutaneous reaction. This reaction was absent in CB_2 receptor deficient mice, and both **JTE-907** and **SR144528** dose-dependently reduced the ear swelling induced by the application of the allergen [198]. Similarly, in oxazolone-sensitized mice, **SR144528** attenuated the recruitment of eosinophils and ear swelling observed in chronic contact dermatitis [199].

Taken together, the above findings strongly support a role for the CB_2 receptors and cannabinoids in mediating inflammation and allergic reactions. The dramatic reduction in the inflammatory/allergic processes obtained with CB_2 receptor antagonists should warrant further research in the field.

4. Looking Forward. – The first selective cannabinoid-receptor antagonists constituted an invaluable tool allowing unraveling the complexity of the endocannabinoid system. Several conditions were identified in which a pharmacological down-regulation of the cannabinoid tone proved to be positive. Of those, the most widely known is the reduction of food intake and improvement of the lipidic and glycaemic profiles in obese patients upon administration of a CB_1 receptor antagonist. Rimonabant is the first compound of this class to receive regulatory approval, and many other compounds are currently in Phase-II or Phase-III trial for this indication. Clinical trials to assess the usefulness of the CB_1 antagonists in treating addictions are underway. Other applications such as the treatment of affective and cognitive disorders

will probably require further work before reaching the clinical-trial phase. On the CB_2 side of the endocannabinoid system, a strong body of evidence is starting to emerge, suggesting that CB_2 antagonists would be a helpful therapeutic tool in treating allergic reactions. The future looks bright for the research on cannabinoid-receptor antagonists.

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