Drugs of the Future 2005, 30(2): 128-137

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.02.880929

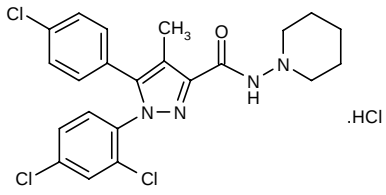
Rimonabant Hydrochloride

Prop INNM

Antiobesity Drug
Aid to Smoking Cessation
Treatment of Alcohol Dependency
Cannabinoid CB_1 Antagonist

SR-141716A
Acomplia™

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)pyrazole-3-carboxamide hydrochloride



$C_{22}H_{21}Cl_3N_4O.HCl$
Mol wt: 500.2548
CAS: 158681-13-1
CAS: 168273-06-1 (as free base)
EN: 217004

Abstract

Obese patients are at a higher risk for coronary artery disease, hypertension, hyperlipidemia and diabetes mellitus, among other diseases, and thus their risk of morbidity and mortality increases. Due to the many complex pathophysiological components which lead to obesity, the disease remains a challenging and significant clinical problem. Cannabinoids acting via cannabinoid receptors stimulate food intake and a particularly attractive antiobesity target is the cannabinoid CB_1 receptor, which has also been shown to play a role in reinforcing reward. Rimonabant hydrochloride (SR-141716A) is a promising CB_1 receptor antagonist that was shown to inhibit motivational and consummatory aspects of feeding, as well as alcohol and nicotine intake in animal models. The agent exhibited efficacy in phase III trials as a treatment for obesity and for smoking cessation. Phase II studies are also under way for the treatment of alcoholism.

Synthesis

Rimonabant can be synthesized by several ways:

1) Claisen condensation of 4'-chloropropiophenone (I) with diethyl oxalate in the presence of lithium hexamethyldisilazide gives 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutyric acid ethyl ester lithium salt (II). Condensation of compound (II) with 2,4-dichlorophenylhydrazine (III) in refluxing ethanol affords hydrazone (IV), which is further cyclized to pyrazole (V) in refluxing AcOH. Hydrolysis of the ethyl ester group of compound (V) with KOH in refluxing H_2O/MeOH yields the carboxylic acid (VI), which is then activated as the acid chloride (VII) by treatment with thionyl chloride. Finally, acid chloride (VII) is coupled with 1-aminopiperidine (VIII) by means of triethylamine in CH_2Cl_2 and treated with HCl in ethyl ether (1, 2). Scheme 1.

2) In an improved procedure, 4'-chloropropiophenone (I) is initially converted to the silyl enol ether (IX) using chlorotrimethylsilane and triethylamine in acetonitrile. Acylation of compound (IX) with ethyl chloroglyoxylate in the presence of $ZnCl_2$ produces the diketo ester (X), which is condensed with hydrazine (III), followed by acid cyclization of the intermediate hydrazone (IV) in refluxing TsOH/toluene to provide pyrazole (V) (1, 2). Scheme 1.

3) Alternatively, condensation of 4'-chloropropiophenone (I) with diethyl oxalate by means of LiHMDS, followed by hydrolysis with HCl gives 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutyric acid ethyl ester (X), which is condensed with 2,4-dichlorophenylhydrazine (III) in refluxing ethanol to yield a mixture of the hydrazone (IV) and the pyrazole ester (V) easily separated by solubility differences. Treatment of hydrazone (IV), pyrazole ester (V), or the mixture of both, with NaOH in refluxing ethanol affords 5-(4-chlorophenyl)-4-methyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid (VI) (3). Scheme 2.

4) Bromination of 4'-chloropropiophenone (I) with Br_2 in AcOH gives α-bromo-4'-chloropropiophenone (XI), which is condensed with ethyl acetoacetate (XII) by means of NaH in refluxing THF to yield the adduct (XIII). Cyclization of compound (XIII) with 2,4-dichlorophenyldiazonium chloride (XIV) by means of Na in ethanol/water at 0 °C affords 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-

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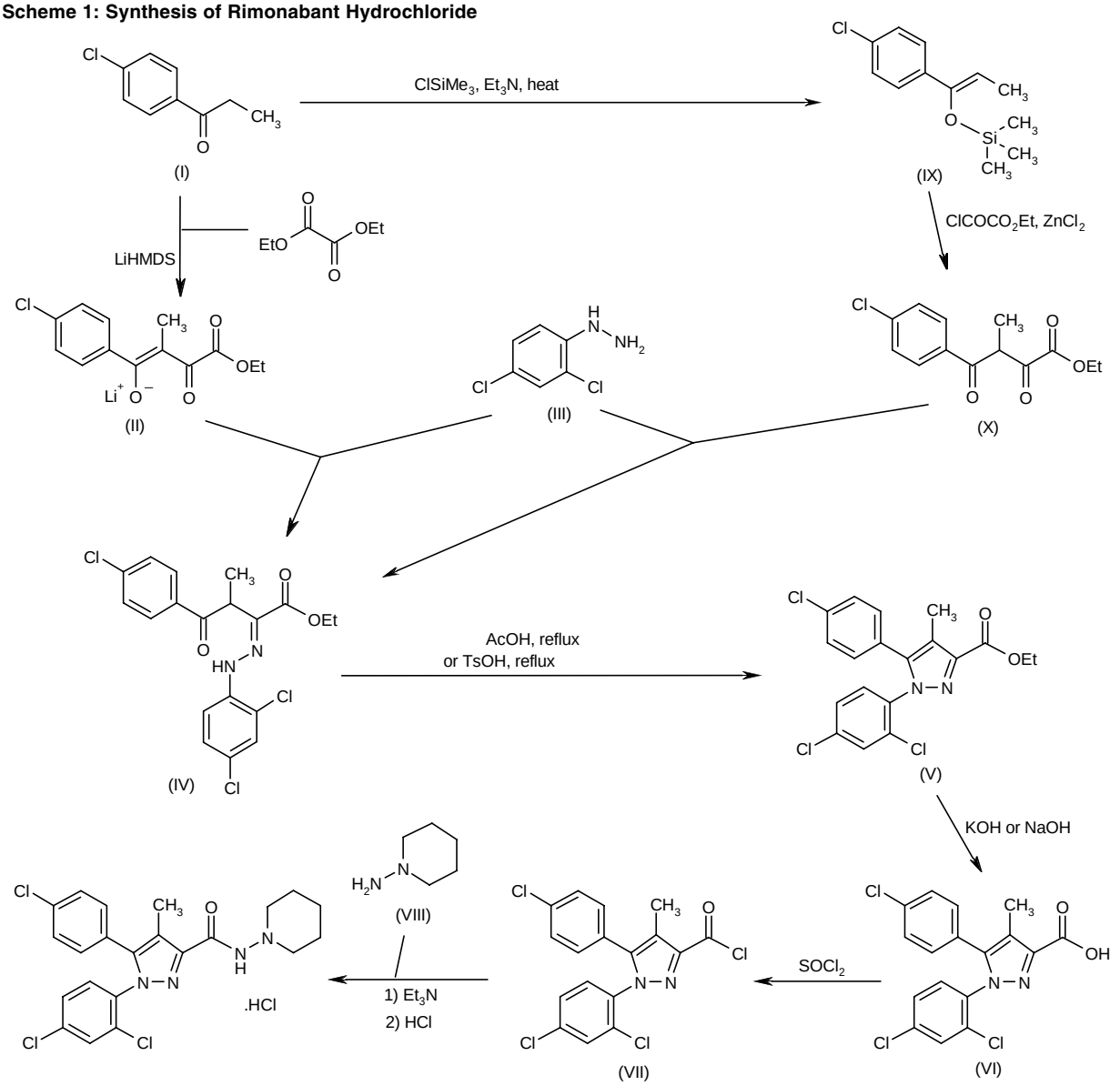
Scheme 1: Synthesis of Rimonabant Hydrochloride



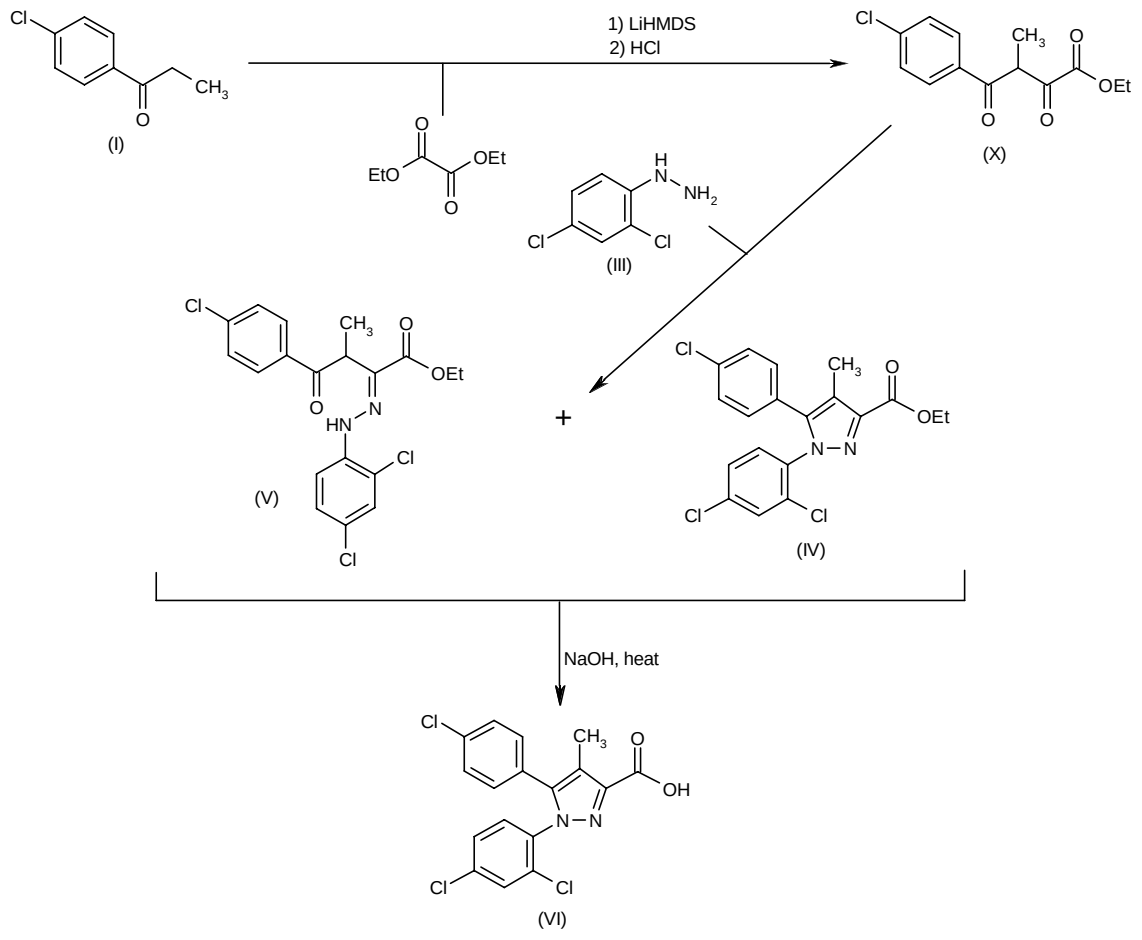
4-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (V), which is treated with NaOH in refluxing ethanol to provide the corresponding free carboxylic acid (VIII). The treatment of acid (VIII) with oxalyl chloride in dichloromethane gives the acyl chloride (IX), which is finally condensed with 1-aminopiperidine and TEA (4). Scheme 3.

Introduction

Obesity is a chronic disorder that has reached epidemic proportions globally. It is a complex, multifactorial metabolic disease defined as an excessive accumulation of fat in adipose tissue such that health and well-being are adversely affected. Obesity develops when energy intake exceeds energy expenditure. According to the Centers for Disease Control and Prevention, nearly two-thirds of the adult U.S. population are overweight (body mass index [BMI] = 25-29.9 kg/m^2) and more than half of these individuals are obese (BMI = 30 kg/m^2 or greater). The World Health Organization (WHO) estimates that more than 700 million adults are overweight and predicts a worldwide obese population of 300 million for the year 2025. Moreover, the number of overweight and obese children and adolescents has doubled over the past 2-3 decades (5-9).

Obese subjects are at a higher risk for coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus,

Scheme 2: Synthesis of Intermediate VI



cancer, cerebrovascular events, osteoarthritis, restrictive pulmonary disease and sleep apnea. The risk of morbidity and mortality increases with a BMI exceeding 27 kg/m^2 and with an increase in waist circumference. Obesity increases mortality, and in the U.S. alone, about 300,000 deaths a year are associated with excess weight and obesity (6, 10-12).

Due to the many complex pathophysiological components believed to play a role in the development of obesity, the disease remains a challenging and significant clinical problem. Diet and exercise as a treatment for obesity have a low overall success rate. Pharmacotherapy currently available for the treatment of obesity includes only 2 compounds: orlistat, a fatty acid synthase inhibitor, and sibutramine, an inhibitor of serotonin and norepinephrine reuptake. Unfortunately, these agents produce only a modest weight loss of 2.6-4.8 kg. Thus, there is an ongoing need for more effective antiobesity agents (5).

Several peptides and neurotransmitters have been found to have acute or chronic effects on feeding behavior and represent exciting new targets for the development of antiobesity agents. These targets and their effects on food intake (*i.e.*, stimulation or inhibition) are shown in Table I.

Studies have shown that treatment with cannabinoids which act via the cannabinoid CB_1 or CB_2 receptor stimulate food intake in rats (13, 14). One particularly attractive target is the cannabinoid CB_1 receptor, a G-protein-coupled receptor widely distributed in the brain and peripheral organs, including adipose tissue and gastrointestinal, pulmonary, reproductive and cardiovascular systems, which appears to be involved in the regulation of energy balance and body weight, as well as in reinforcing reward. Antagonism of this receptor could therefore be effective in decreasing food intake (15). Cannabinoid CB_1 receptor antagonists currently under active development for the treatment of obesity are shown in Table II.

Scheme 3: Synthesis of Rimonabant Hydrochloride

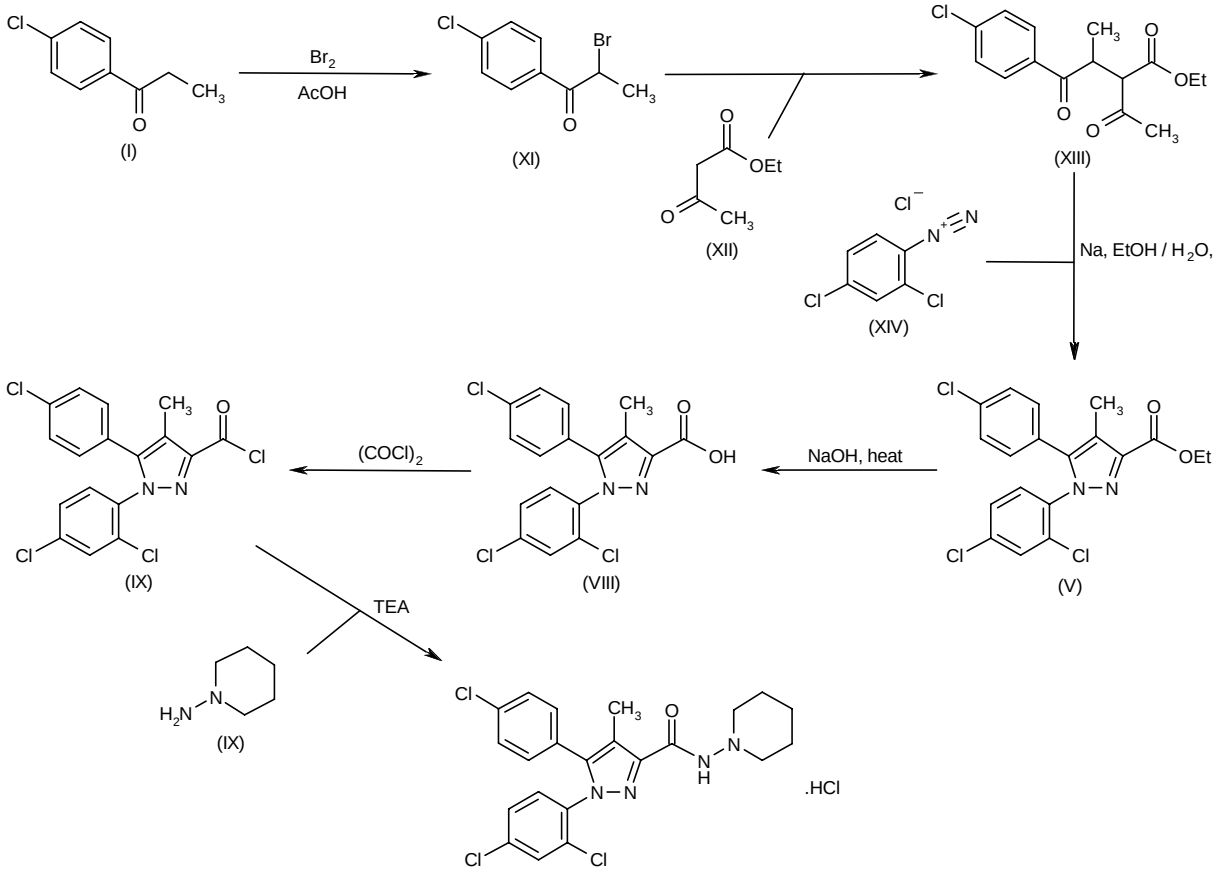
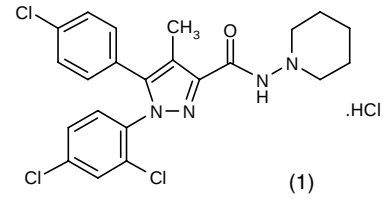


Table I: Targets for the development of antiobesity agents (from Prous Science Integrity®).

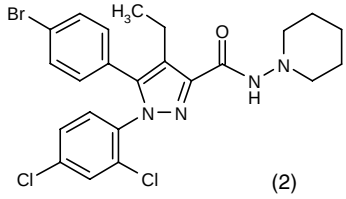
Targets stimulating food intake	Targets inhibiting food intake
ATP citrate synthase	β_3-Adrenoceptor
Agouti-related protein (AgRP)	Carnitine *O*-palmitoyltransferase-1 (CPT-1)
Cannabinoid CB_1 receptor	CART (cocaine and amphetamine-regulated transcript) receptor
Corticotropin-releasing factor CRF_1 receptor	Cholecystokinin CCK_1 receptor
Galanin	Ciliary neurotrophic factor (CNTF)
Ghrelin	Corticotropin-releasing factor CRF_2 receptor
Histamine H_3 receptor	Glucagon-like peptide-1 (GLP-1)
11-β-Hydroxysteroid dehydrogenase type 1 (11-β-HSD1)	Growth hormone
Fatty-acid synthase	IL-6
Melanin-concentrating hormone MCH1 receptor	Leptin
Neuropeptide Y (NPY) Y_1 and Y_5 receptors	Melanocortin MC_4 receptor
Opioid receptors	α-Melanocyte-stimulating hormone (α-MSH)
Orexin-1 receptor	Neuromedin U receptor 2 (NMUR2, FM-4)
Protein-tyrosine-phosphatase PTP1B	Neuropeptide Y (NPY) Y_2 receptor
5-HT_6 receptor	Oxyntomodulin
Triacylglycerol lipase	Peptide YY (PYY)3-36
Tripeptidyl-peptidase II	Peroxisome proliferator-activated receptors PPARα/γ and δ
	PPARγ coactivator-1 (PGC-1)
	5-HT_{2C} receptor
	Thyroid hormone receptor-β_1 (THRB)
	Urocortin I

Table II: Cannabinoid antagonists under active development for the treatment of obesity.

Compound	Phase	Source
1. Rimonabant Hydrochloride	III	Sanofi-Aventis
2. SR-147778	I	Sanofi-Aventis
3. SLV-319	I	Solvay/Bristol-Myers Squibb
4. SLV-326	Prelinical	Solvay



(1)



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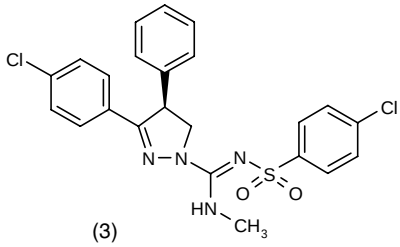

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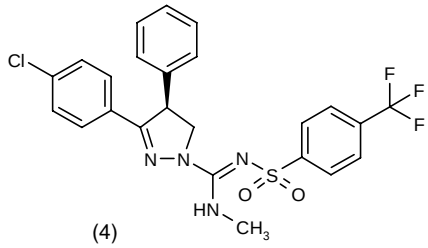

(4)

Table III: Human cannabinoid receptor affinities and CB_1 selectivity of selected CB_1 antagonists under active development (from Prous Science Integrity®).

Compound	CB_1	CB_2	CB_1 selectivity	Refs.
	K_i (nM)		$K_{i\,(CB2)}/K_{i\,(CB1)}$	
Rimonabant	13.3 ± 3.1	1638±782	123.2	16, 40-47
SLV-319	7.8	7943	1018.3	41
SLV-326	10.0	1995	119.5	48
SR-147778	3.5	442	126.3	49

Mean±s.e.m. calculated from individual values from different studies using cloned human receptors.

Rimonabant hydrochloride (SR-141716A) is a promising CB_1 receptor antagonist with potent and selective activity in binding and functional assays (Tables III and IV), and which has been shown to inhibit motivational and consummatory aspects of feeding and reduce alcohol and nicotine intake in animal models. Rimonabant was therefore chosen for further development as a treatment for obesity and alcoholism, and for use in smoking cessation.

Pharmacological Actions

Early *in vivo* studies in mice demonstrated that rimonabant binds to the CB_1 receptor. Intraperitoneal administration of the agent to mice did not alter body weight or locomotor activity. However, pretreatment with rimonabant (1 mg/kg i.v.) suppressed the hypothermic effect (100%) and hypoactivity (68%) caused by the psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC; 1 mg/kg), as well as the hypothermic effects (ED_{50} = 0.23 mg/kg i.p.) of the aminoalkylindole cannabinoid WIN-55,212-2 (4, 16).

Rimonabant suppressed food intake in several *in vivo* studies. When administered as a daily dose of 2.5 or 10 mg/kg i.p. to nonobese adult rats, rimonabant dose-dependently reduced food intake (25% and 50%, respectively) and body weight. Tolerance was observed after 5 days of administration, although the reduction in body weight was sustained in rimonabant-treated animals through the 14-day experimental period. Water intake was not altered by treatment (17).

While significant appetite-suppressing effects were observed in wild-type $CB^{+/+}$ mice treated with a single dose of rimonatant (3 μg/g i.p.) in another study, no effects were observed in $CB^{-/-}$ knockout mice (18). Similarly, treatment of $CB^{-/-}$ mice with rimonabant (10 mg/kg/day p.o.) for 3 weeks had no effect on food intake or body weight. In contrast, significant reductions in body weight (34.6 ± 1 g *vs.* 41.5 ± 0.7 g after 21 days) and

Table IV: Functional activities of selected cannabinoid CB_1 receptor antagonists under active development (from Prous Science Integrity®).

	In vitro assays			*In vivo* assays		
	Arachidonic acid release (WIN-55212-2-induced) inhibition[a]	Muscle contraction (electrically induced/CP-55940-depressed) antagonism[b]	cAMP production (forskolin-induced/ CP-55940-depressed) antagonism[c]	Hypothermia WIN-55212-2 induced) inhibition[d]	Vasodepression (agonist-induced) inhibition[e]	Refs.
Compound	pA_2		pIC_{50}	ED_{50} or MED* (mg/kg p.o.)		
Rimonabant	8.6	7.98 ± 0.30	8.25[1]	0.15[3] 0.38[4]	3.2[5]	16, 41
SLV-319	9.9	–	–	3.0[4,*]	5.5[5]	41
SLV-326	9.1	–	–	1.0[3,*]	2.2[6]	48
SR-147778	–	8.06 ± 0.13	8.03[2]	0.40[4]	–	49

[a]Arachidonic acid release assay conducted in CHO cells transfected with cloned human CB_1 receptors; [b]Muscle contraction antagonism assay in mouse vas deferens; [c]cAMP production antagonism assay in [1]CHO cells transfected with cloned human CB_1 receptors or in [2]U-373 MG human astrocytoma cells constitutively expressing CB_1 receptors; [d]Hypothermia evaluated in either [3]rats or [4]mice; [e]Vasodepression assay in rats using [5]CP-55940 or [6]WIN-55212-2 as agonist.

energy intake (9.6 ± 0.5 kcal/day *vs.* 15.2 ± 0.4 kcal/day during week 1) were observed in wild-type $CB^{+/+}$ mice as compared to untreated wild-type controls. Wild-type animals treated with the agent also had significantly lower weights of lumbar fat masses as compared to untreated wild-type controls (0.299 ± 0.037 g *vs.* 0.526 ± 0.03 g); again, no effect was observed in rimonabant-treated $CB^{-/-}$ mice. Wild-type mice fed a high-fat diet and treated with the agent exhibited significantly lower plasma insulin levels compared to untreated wild-type animals also fed a high-fat diet (2.16 ± 0.39 ng/ml *vs.* 6.94 ± 1.51 ng/ml). This effect on insulin levels was not observed in $CB^{-/-}$ mice fed a high-fat diet and treated with rimonabant (19).

Rimonabant (0.03-3 mg/kg i.p.) was shown to significantly suppress food intake in rats regardless of the composition of the food. Nonfasted rats were administered a high-fat, a high-carbohydrate or a normal chow diet. Food intake, regardless of the composition, was significantly suppressed following administration of the agent for the 120-min examination period. Locomotion was not affected. Thus, food deprivation and high palatability of food do not influence the suppressive effects of rimonabant (20).

Rimonabant (0.5-8 mg/kg once weekly 30 min before testing) was effective in suppressing food intake and food-reinforced behavior in rats. Dose-dependent reductions in lever pressing were observed in rimonabant-treated animals and effects were sustained for a relatively long period ($t_{1/2}$ = 15.1 h). Effects of the agent were similar in rats given a high-fat, a high-carbohydrate or a normal chow diet and in food-deprived and nondeprived rats (21).

In a similar study, the significant and dose-dependent reductions in lever pressing in rimonabant (0.3-3 mg/kg i.p.)-treated trained rats were significantly attenuated when animals were pretreated with the CB_1 agonist WIN-55,212-2 (0.3 mg/kg). These results confirm that the CB_1 receptor mediates the appetite-suppressing effects of the agent in this model (22).

Rimonabant (1-3 mg/kg i.p. or p.o.) was shown to have an additive and supra-additive anorectic effect when administered together with dexfenfluramine (0.5-4 mg/kg) and naloxone (0.5-2.5 mg/kg), respectively, to rats trained to eat a palatable sweet milk dessert or normal chow. Rimonabant had no effect on water intake and no tolerance to the agent was observed over 3 days. These results suggest a synergistic and additive interaction between serotonin and opioid systems, respectively, and the cannabinoid systems in feeding regulation (23).

The anorectic efficacy of rimonabant was also evident in diet-induced obese mice and obese (*fa/fa*) and lean Zucker rats. Treatment of diet-induced obese mice with the agent (10 mg/kg/day p.o.) for 5 weeks transiently decreased food intake (48% during week 1), but produced significant and sustained reductions in body weight (20%) and adiposity (50%). Rimonabant corrected insulin resistance and lowered plasma leptin, insulin and free fatty acid levels; similar but lesser effects were observed with a dose of 3 mg/kg/day. Rimonabant had no effect in $CB^{-/-}$ mice with diet-induced obesity. It was suggested that, in addition to inducing hypophagic effects, rimonabant may also influence metabolic processes since the reduction in body weight in rimonabant-treated mice was significantly greater than in untreated animals during 24 h of fasting (24).

Rimonabant (3, 10 or 30 mg/kg p.o.) dose-dependently decreased food intake and body weight gain in both lean and obese Zucker rats, although a greater effect was observed in obese animals. Dose-dependent induction of motor behaviors (*e.g.*, withdrawal signs such as wet dog shakes and scratching) were observed with acute administration, although tolerance developed after repeated dosing. Chronic treatment (1, 3 or 10 mg/kg p.o. for 28 days) resulted in a sustained reduction in body weight with rebound hyperphagia and significant weight gain observed after drug withdrawal. Chronic treatment with the agent also significantly reduced water intake in this study (25).

Chronic treatment with rimonabant (10 mg/kg/day p.o. for 10 weeks) in mice fed a high-fat diet for 5 months, resulting in established obesity, caused a sustained and significant reduction in body weight as compared to vehicle-treated controls (34.5 ± 0.8 g *vs.* 47.2 ± 0.5 g); a transient reduction (14 days) in energy intake was observed with treatment. This effect was similar to the weight reduction seen after obese mice were switched from a high-fat diet to a standard diet for 10 weeks (final weight = 33.7 ± 0.6 g). Treatment with rimonabant also significantly reduced the obesity-induced increases in serum leptin (–81%), insulin (–78%) and glucose (–67%) levels, and significantly increased serum adiponectin (+18%). Moreover, the agent significantly decreased triglyceride and LDL cholesterol without affecting HDL cholesterol, leading to a significant increase in the HDL cholesterol/LDL cholesterol ratio (12.4 ± 0.8 *vs.* 7.9 ± 0.2) (26).

Rimonabant proved effective in marmosets, where doses of 1 and 3 mg/kg p.o. decreased feeding of a highly palatable cane sugar mixture; the lower dose did not reduce standard primate pellet intake, but instead significantly and slightly increased intake (29%) (27).

Several studies have demonstrated that rimonabant reduces alcohol and nicotine consumption, indicating possible efficacy as a treatment for alcohol and nicotine dependence.

Rimonabant (0.15, 0.3 or 0.6 mg/kg i.p.) administration decreased beer consumption in a continuous-access paradigm in rats. Synergistic effects in reductions in motivation to consume alcohol were observed when the lowest dose of rimonabant was combined with naloxone (0.3 mg/kg i.p.); a combination using the highest dose of rimonabant and 1.2 mg/kg naloxone produced additive suppressive activity. Treatment with either agent alone or in combination was more effective than allowing access to near-beer. Results suggest that rimonabant reduces alcohol craving (28).

Rimonabant was shown to decrease the motivational properties of alcohol in Sardinian alcohol-preferring rats trained to lever-press for alcohol. Extinction responding for alcohol (*i.e.*, the maximum number of lever responses in the absence of alcohol) was dose-dependently and almost completely abolished following administration of the agent (0.3, 1 and 3 mg/kg i.p.), whereas no effect was seen on extinction responding for sucrose. In a similar study, acute treatment of Sardinian alcohol-preferring rats with rimonabant (0.3, 1 and 3 mg/kg i.p.) abolished the effects of alcohol deprivation, in contrast to untreated animals which voluntarily doubled alcohol consumption during reaccess to alcohol. Together, these results suggest that the agent may be effective as a treatment for alcoholism (29, 30).

The effects of rimonabant on the motivational effects of nicotine were also examined in rats. Pretreatment with the agent (0.3 and 1 mg/kg i.p.) decreased nicotine self-administration but did not substitute (0.3-3 mg/kg i.p.) for nicotine or antagonize the nicotine cue in nicotine discrimination procedures. However, when administrated to rats trained to discriminate D-amphetamine, rimonabant (0.01-1 mg/kg i.p.) dose-dependently blocked the substitution of nicotine for D-amphetamine. Brain microdialysis studies revealed that the agent (3 mg/kg i.p. 30 min before nicotine or alcohol administration) blocked nicotine (0.4 mg/kg s.c.)- and alcohol (1 g/kg i.p.)-induced dopamine release in the shell of the nucleus accumbens and nicotine-induced dopamine release in the bed nucleus of the stria terminalis. From these results, it was suggested that the endogenous cannabinoid system may play a role in the motivational and dopamine-releasing effects of nicotine and alcohol, and that rimonabant may therefore be effective in reducing alcohol intake and aid in the cessation of smoking (31).

Two different studies have demonstrated that rimonabant may be effective not only in aiding in smoking cessation, but also in the maintenance of abstinence from smoking. A study conducted in rats trained to selfadminister nicotine (0.03 mg/kg/injection i.v.) in a paradigm in which response was reinforced by response-contingent nicotine injections and audiovisual stimuli (light and tone), administration of rimonabant (1 mg/kg i.p.) 1 month after nicotine withdrawal decreased conditioned behavior. Similarly, acute administration of rimonabant (1 or 3 mg/kg i.p.) blocked the expression of nicotine-induced conditioned place preference in rats and had no effect on nicotine-like discriminative effects or the dose-response curve for nicotine discrimination in rats trained to discriminate nicotine from saline. Thus, treatment with rimonabant selectively decreased the influence of environmental stimuli that could lead to persistent smoking behavior (32, 33).

Clinical Studies

The efficacy and safety of rimonabant (5, 10 or 20 mg once daily for 16 weeks) were examined in a randomized, placebo-controlled trial which included a 2-week, single-blind placebo run-in period and involved 287 obese male and female subjects (BMI = 29-41 kg/m^2) on a mildly hypocaloric diet (500 kcal deficit daily). The safety profile of the agent was considered satisfactory. Significant reductions in mean body weight of 2.5, 2.7 and 3.8 kg were observed for doses of 5, 10 and 20 mg rimonabant, respectively, as compared to 0.9 kg for placebo. Significant reductions in waist circumference were also observed in the highest dose group as compared to placebo (3.9 cm *vs.* 1.1 cm); the groups receiving 5 and 10 mg rimonabant also exhibited decreases in waist circumference (2.6 and 2.5 cm, respectively), although this was not significant (34).

Results from RIO-Lipids, a 1-year, multicenter, randomized, double-blind, placebo-controlled phase III study, demonstrated the efficacy and safety of rimonabant (5 or 20 mg once daily) in reducing body weight and obesity-related metabolic risk factors. RIO-Lipids is the first of 4 phase III studies conducted in a total of over 6,000 overweight/obese subjects. RIO-Lipids involved 1,036 overweight/obese subjects (mean weight = 96.1 kg,

mean waist circumference = 107.1 cm) with a BMI > 27 kg/m^2 (mean BMI = 34 kg/m^2), untreated dyslipidemia (triglyceides > 1.69 mmol/l and/or total cholesterol/HDL cholesterol > 4.5 and 5 for males and females, respectively) and fasting glucose levels of < 6.99 mmol/l. The subjects were randomized to receive placebo or rimonabant and maintained on a mildly hypocaloric diet for 52 weeks. Rimonabant was well tolerated. Results for the 5-mg rimonabant group were either similar to placebo or intermediate between placebo and the 20-mg group. The group receiving 20 mg of rimonabant exhibited significant reductions in body weight (–6.9 kg) and waist circumference (–7.1 cm) as compared to placebo. Of those patients who received 20 mg rimonabant and completed the trial, 72.9% lost more than 5% of their initial body weight as compared to 27.6% on placebo. Significant improvements in overall plasma glucose and insulin responses compared to placebo were observed during oral glucose tolerance tests in the 20-mg rimonabant group. In addition, plasma triglyceride levels were significantly reduced (0.4 mmol/l) and HDL cholesterol levels significantly increased (+0.2 mmol/l). The high-dose group also exhibited significant reductions in plasma leptin (mean difference = –3.8 mg/ml) and increases in plasma adiponectin (mean difference = +1.6 μg/ml). Significant correlations were found in this group between changes in leptin and weight loss and changes in adiponectin levels and changes in HDL cholesterol levels. A decrease from 52.9% to 25.8% in the prevalence of metabolic syndrome according to NCEP-ATPIII criteria was observed in the group treated with the higher dose (35, 36).

Two other phase II studies, RIO-Europe (RIO-EU) and RIO-North America (RIO-NA), are being conducted to examine the efficacy and safety of rimonabant (5 or 20 mg) in weight reduction, weight maintenance and prevention of weight gain over 2 years. The studies are both multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trials with 4-week, single-blind placebo run-in periods, and include 1,507 and 3,044 overweight/obese subjects (mean BMI = 36.6 kg/m^2; mean weight = 102.7 kg; mean waist circumference = 109.9 cm), respectively, with or without comorbidities who were prescribed a mildly hypocaloric diet throughout the study. Subjects with type 2 diabetes were excluded from the study. In the RIO-EU study, 41%, 61% and 41% of the subjects were hypertensive, had dyslipidemia and met NCEP-ATPIII criteria for metabolic syndrome, respectively. The primary efficacy endpoints of both studies were weight loss and weight maintenance at 1 year; prevention of weight gain during the second year was a primary endpoint for the RIO-NA trial only. Secondary outcomes included lipid concentrations, oral glucose tolerance tests and fasting glucose/insulin level homeostasis. Analysis of data is ongoing for these trials. A fourth study (RIO-Diabetes) conducted in obese patients with type 2 diabetes receiving biguanide or sulfonylurea monotherapy has also been initiated (37, 38).

A multicenter, double-blind, placebo-controlled phase III trial randomized 784 smokers (at least 10 cigarettes/day) to receive rimonabant (5 or 20 mg/day) or placebo together with brief weekly counseling. The primary endpoint was prolonged abstinence during the last 4 weeks of treatment. Secondary outcomes were body weight change and safety and tolerability of the agent. Rimonabant was well tolerated, few subjects discontinuing due to adverse events. A significantly greater 28-day, biochemically verified smoking abstinence rate (27.6% *vs.* 16.1%) was observed in the group receiving 20 mg rimonabant as compared to placebo. In addition, a significant difference in body weight change was observed in the 20-mg group compared to placebo (–0.3 kg *vs.* +1.1 kg). A greater difference in body weight was observed when only nonobese subjects with prolonged abstinence were included (+0.7 kg *vs.* +3 kg). Thus, a 77% reduction in post-cessation weight gain was observed in nonobese subjects who had quit smoking and were treated with 20 mg rimonabant. The safety and efficacy of rimonabant as a treatment for nicotine dependence continue to be investigated in the ongoing phase III STRATUS Europe and STRATUS Worldwide trials (39).

Source

Sanofi-Aventis (FR).

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